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Sudden unexpected death in epilepsy : incidence, circumstances & mechanisms.

SUDDEN UNEXPECTED DEATH IN EPILEPSY

INCIDENCE, CIRCUMSTANCES & MECHANISMS

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Synopsis

This dissertation addresses the incidence, circumstances and possible mechanisms of sudden unexpected deaths (SUDEP) within the context of overall excess mortality in patients with chronic epilepsy.

Mortality data is presented from two selected cohorts. Standardised mortality ratio was 5.1 (95% CI 3.3-7.6) in an outpatient cohort of 601 patients (1849 person years) at a tertiary referral centre, and 15.9 (95% CI 10.6-23.0) in a young cohort with epilepsy and learning difficulty (310 persons and 4135 person years). Excess mortality was mainly related to the epilepsy itself rather than to underlying disease. SUDEP incidence of 1:200/year and 1:295/year was observed in each cohort respectively.

In a separate study, 27 interviews of self-referred bereaved relatives of cases of sudden unexpected deaths were conducted. Of twenty cases who fulfilled the definition of SUDEP (page 17), 19 were unwitnessed with circumstantial evidence suggestive of a seizure found in the majority. Perceived needs of bereaved relatives were also explored.

In a study of ictal cardiorespiratory changes, apnoea was recorded in 10/17 patients or 20/47 clinical seizures (3 secondary generalised, 16 complex partial and 1 tonic). The

apnoea was mainly central although obstructive apnoea was also recorded. An increase in heart rate was commonly observed occurring in 91% of seizures. Bradycardia/sinus arrest occurred in at least 4 patients (mean maximum RR interval 5.36s, range 2.8-8.6) within the context of a change in respiratory pattern. In 3 cases this occurred during an apnoeic spell. SpO2 dropped to less than 85% in 10 seizures (6 patients).

In summary, a relatively high incidence of SUDEP is shown in 2 large selected cohorts with chronic epilepsy. Evidence is presented supporting the view that SUDEP cases are in the main unwitnessed seizure-deaths. Apnoea, which may be central or obstructive, is shown to be common during seizures. The occurrence of bradycardia in association with apnoea suggests that cardiorespiratory reflexes, known to be more pronounced in young people, may play a role in sudden death in epilepsy.

Declaration

This thesis is the result of my own independent work carried out while a research fellow with the Epilepsy Research Group, Institute of Neurology, Queen Square London and the National Society for Epilepsy, Chalfont St Peter between December 1992 and October 1994.

Contributions of colleagues towards the project are clearly specified in the acknowledgements and where appropriate in the text. Related publications and preliminary findings published in abstract form are listed in the appendix.

Local ethical committee approval was obtained for all aspects of this work.

Lina Nashef, February 1995

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The Office of Population Censuses and Surveys (Southport) helped in tracing persons lost to follow-up. I am also

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Lina Nashef

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Terminology & Abbreviations

AED	Antiepileptic Drugs
bpm	Beats per minute
brpm	Breaths per minute
95% CI	95% Confidence Intervals
CPS	Complex Partial Seizures
ECG	Electrocardiography
EEG	Electroencephalography
EMG	Electromyogram
EOG	Electrooculogram
TCS	Generalised Tonic Clonic Seizure
Hb	Haemoglobin
ILAE	International League Against Epilepsy
IHD	Ischaemic heart disease
IQ	Intelligence Quotient
JME	Juvenile myoclonic epilepsy
n	Number
OPCS	Office of Population Censuses and Surveys
p	Probability
p.m.	Post-mortem examination
s	Seconds
SMR	Standardised Mortality Ratio
SpO2	Percentage (O2) saturation of haemoglobin
Yr(s)	Year(s)

SUDEP: Sudden, unexpected, witnessed or unwitnessed, non-traumatic & non-drowning death in epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, where post-mortem examination does not reveal a toxicological or anatomical cause for death

INTRODUCTION

Preface

One hundred years ago the potential for an epileptic seizure to end life was acknowledged. Epileptologists in the nineteenth and early twentieth century described mortality in epilepsy from epilepsy. Following two world wars, the subject was addressed again, but the setting had altered and new writers did not pick up where others had left off. Effective modern antiepileptic drugs meant that physicians felt both optimistic and omnipotent. Patients with epilepsy had moved out of asylums into the community and there was much less opportunity for direct observation. Risks from epilepsy were minimised then denied; that seizures could not be fatal became 'common knowledge' despite evidence to the contrary.

Even today, whether through ignorance or reluctance, the subject is often overlooked.

1. Background Information

1.1 Overview of Mortality in Epilepsy[1]

1.1.1 Introduction

In writing his textbook on prognosis, Rodin (1968) expressed misgivings in addressing outcome. Given that epilepsy was not considered a disease but a symptom of a variety of illnesses, what was the sense in writing about prognosis? Yet, epilepsy has its own consequences; it is both a symptom and a disease, and seizures have implications beyond those of their underlying cause. With advances in treatment, and in an attempt to minimise restrictions, epilepsy has come to be regarded as benign with consequences of seizures underplayed. The pendulum may have swung too far. Mortality in patients with epilepsy is increased 2 to 3 times that of the general population. Broadly speaking the reason for excess mortality in epilepsy differs in recent onset and in chronic cases. In the former this is mainly due to underlying disease, and in the latter excess deaths are primarily epilepsy related.

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[1] This section includes material written for Recent Advances in Epilepsy (6) and is included here with the publisher's permission (Churchill Livingstone)

1.1.2 Overall National Mortality Data

G Mackenzie Bacon (1868) suggested that once cases with known secondary epilepsy were excluded, causes of death may be categorized as follows: *"1. Those arising from the long continued effects of the disease on the body; 2. Deaths after a rapid succession of fits; 3. Sudden deaths in a fit; 4. Accidents due to fits.'* He added that *'if practitioners would adopt some such system...we should not have to lament such a meaningless blank as the word now represents in lists of mortality'.*

The situation is similar today. National mortality data have made but small contribution to the study of mortality in epilepsy. 906 deaths in England and Wales (1.78/100,000 of population) in 1991 were listed as due to epilepsy (Office of Population Censuses and Surveys). Apart from the subheading of status epilepticus, this figure is not usefully subdivided. Based on the International Classification of Diseases Code, listed causes of death are entirely dependant on death certificate completion and inconsistencies thereof. Epilepsy was recorded in only 74% of certificates in Warsaw where death was due to epilepsy (Zielinski 1974).

Similar gross national figures have been obtained from other countries (Chandra et al 1984 a&b, Jallon et al 1989) and compared between different countries and different

epochs (Massey & Schoenberg 1985). Reported rates range from 0.6 - 4.0 deaths/100,000 per year. Inaccuracies in death certification coupled with doubt about the way cases are ascertained and causes ascribed render these figures fairly meaningless.

1.1.3 Underlying Disease & Epilepsy - Influence on Mortality

Mortality in epilepsy has been shown in most (Hauser et al 1980, Henriksen et al 1970, Zielinski 1974) but not all studies (Schwade & Otto 1954) to be increased compared with the general population. The subject has been reviewed by Hauser & Hesdorffer (1990) who, in contrast to earlier writers (Bacon 1868, Munson 1910) emphasize the excess mortality due to underlying disease. They state that: 'Studies suggest that the underlying conditions, rather than the epilepsy itself may explain most of the increased relative risk in younger patients.'

In support of this view, and reflecting the fact that epilepsy is secondary to a number of disease processes, is the observation, in longitudinal studies, that mortality is highest in the first few years after diagnosis (Hauser et al 1980, Cockerell 1994a). However mortality is also elevated when patients with idiopathic epilepsy are considered separately (Hauser 1980, Henriksen 1970). Excess mortality is likely to be related not only to underlying disease but also to epilepsy per se.

1.1.4 Impact of Mortality on Prevalence of Epilepsy

The prevalence of epilepsy (approximately 0.5%) depends on incidence (approximately 0.05% annually), remission and mortality. Remission has been considered the significant factor in accounting for the difference between cumulative incidence and prevalence. A significant contribution of excess mortality has been discounted (Juul-Jensen & Foldspang 1983) except with reference to developing countries (Sander 1993). However, in a recent on-going comprehensive population-based longitudinal incidence study (Sander et al 1990), of 564 definite cases 114 have already died with an all-cause standardised mortality ratio (SMR - table 1) of 3.0 and a mean follow-up of 6.9 years (3712 person years) (Cockerell et al 1994a).

Table 1: Standardised & Proportional Mortality Ratios

- Standardised mortality ratio: the ratio of deaths observed in a group to the numbers of deaths that would be expected to have occurred during a follow-up period if the group in question had experienced the same age and sex-specific death rates as in the control population.

- Proportional mortality ratio: the proportion of deaths due to a specific cause amongst a study population compared with a control group.

It is of interest to briefly consider the developing world in this context. Incidence rates may be higher owing to a higher risk of symptomatic epilepsy and the age-structure of the population (Shorvon & Bharucha 1993). Treatment rates, on the other hand, based on drug supply figures and field surveys are very low at 1.6%-20% (Shorvon & Bharucha 1993). Although spontaneous remission does occur, rates are lower in untreated groups (Sander 1993). Thus, in developing countries lower remission and higher incidence may be expected to lead to higher prevalence. Yet, except in selected populations, prevalence rates remain comparable at around 0.5% ((Shorvon & Bharucha 1993, Sander 1993), and although these may only be gross estimates with uncertainty about complete case-ascertainment, mortality may be a factor in accounting for the discrepancy. A recent community-based investigation of mortality from Kenya (Snow et al) showed a higher than expected prevalence of reported epilepsy among recently deceased young adults in a population where the use of antiepileptic medication was only sporadic. Interestingly many of the deaths were reported to be due to status epilepticus as judged by reported duration of seizures.

Table 2: (A) Mortality Series in Epilepsy

A. Some mortality series based on cohorts with epilepsy

- general population

  NGPSE, UK, Cockerell et al 1994a

  Rochester, USA, Hauser et al 1980

  Warsaw, Poland, Zielinski 1974

- residents in institutions

  Finland, Iivanainen & Lehtinen 1979

  Chalfont, UK, Klenerman et al 1993

  Craig Colony, USA, Munson 1910

  Chalfont, U.K., White et al 1979

  Warsaw, Poland, Zeilinski 1974

- clinical series

  Denmark, Henriksen et al 1970

  Lausanne, Switz., Penning et al 1969

  Sweden, Brorson & Wranne 1987

  France, Chevrie & Aicardi 1978*1

- insurance company series*2

1 series based on cases with convulsions during the first year of life

2 as quoted by Hauser for a number of countries 1990

Table 2: (B) Mortality Series in Epilepsy

B. Some mortality series based on deaths in epilepsy

- national mortality data/ based on death certificates

USA, Chandra 1984

France, Jallon et al 1989

USA, Satishchandra 1988

International, Massey & Schoenberg 1985

- coroner's post-mortem series

USA, Freytag & Lindenberg 1964

Denmark, Lund & Gormsen 1985

- clinical series

Norway, Krohn 1963

Japan, Hashimoto et al 1989

1.1.5 Selected & Unselected Series

Table 2 (A & B) lists and classifies some of the studies reported on mortality. Different approaches have made difficult comparisons between different studies. Problems of definition and limitations of epidemiological studies in epilepsy have been reviewed (Sander & Shorvon 1987, Zielinski 1988). Death-certificate based studies may underestimate mortality from or related to epilepsy although false positives may also occur (Hauser 1980). Similarly conclusions from selected cohorts cannot be extrapolated to the majority with epilepsy or to other selected groups.

Population-based series are widely considered to be the most informative. Calculations based on deaths per person-years are compared to national all-cause mortality data. The assumption is made that cases lost to observation have the same experience as those remaining. This may not be justified in mortality studies, and not all series clearly report on patient years lost to follow-up.

Furthermore, while invaluable in defining the overall problem, population studies give limited information in terms of defining prognosis in individual cases. Broad categories (cryptogenic/idiopathic, remote symptomatic,

acute symptomatic, or associated with congenital/perinatal neurological abnormality) are used in surveys in view of the inevitably incomplete clinical information in such studies. Nevertheless, even though the categories are based on presumed causation, they do not reflect conceptual developments in the classification of epilepsy syndromes, nor indeed improved imaging techniques which allow for more accurate diagnosis. It is with reference to cases with cryptogenic/idiopathic epilepsies which constitute the largest single category in general population-based studies that this is most relevant.

Prospective population-based studies of selected cohorts with well-defined diagnostic categories are lacking. Such studies may address the relative contributions of seizure type, severity and frequency as well as treatment options within a diagnostic category.

1.1.6 Variables Affecting Excess Mortality

Within the often quoted SMR of 2-3 in patients with epilepsy is a wide range from no increased risk to an SMR of 8 or more. Studies to date suggest that the following factors may influence mortality.

1.1.6.1 Age

The excess observed mortality in patients with epilepsy

decreases with increasing age remaining above that of the general population (Zielinski 1974, Hauser & Hesdorffer 1990, Luhdorf et al 1987). They may simply reflect epilepsy deaths being lost within much higher mortalities from other causes. Luhdorf et al (1987) studied mortality in a cohort with epilepsy over the age of 60 and found an increased mortality in patients with established epilepsy, in patients with new-onset secondary epilepsy, but not in patients with new-onset epilepsy and no identified cause. In young age-groups increased mortality in epilepsy when associated with neurodeficit also needs to be considered.

1.1.6.2 Sex

Excess mortality in epilepsy is reportedly higher in males (Hauser et al 1980, Henriksen et al 1970). The contribution of accidental deaths generally more common among males (Office of Population Censuses and Surveys) is unknown. Occasional higher SMR's are quoted in young females (Zielinski 1974) probably reflecting the particularly low mortality for females aged 1-34 in the general population in the developed world.

1.1.6.3 Race

A higher mortality is reported in the USA for the non-white as compared to the white population with epilepsy (Chandra et al 1984a). This needs to be considered in the context of

lower socioeconomic status and possible higher prevalence rates of epilepsy among Afro-Americans (Haerer 1986, Sander & Shorvon 1987).

1.1.6.4 Seizure Type & Diagnostic Category

Absence seizures are not reported to be associated with higher mortality while generalised tonic clonic and myoclonic seizures are. Complex partial seizure do not appear to carry an additional risk (Hauser et al 1980, Henriksen 1970). Henriksen (1970) reported that patients who at follow-up had severe and moderately severe epilepsy (in terms of seizure-frequency) showed a statistically significant higher mortality as compared to seizure-free and slight cases. Patients with remote symptomatic epilepsy have a higher excess risk compared to patients with cryptogenic/idiopathic epilepsy (Hauser et al 1980, Luhdorf et al 1987).

1.1.6.5 Mental Handicap

It is generally considered that mortality is higher in epilepsy when associated with mental handicap, however, there are often co-existing neurological signs and the two are usually combined (Brorson & Wranne 1987). Mental handicap in general is also associated with a higher risk of accidents (Williams 1973).

Table 3: Death in Epilepsy

Apparently unrelated, for example
- malignancy outside the central nervous system
- accidents not as a consequence to seizures
Related to underlying disease, for example
- brain tumours
- cerebrovascular disease
- cerebral infection
Related directly or indirect to epilepsy
- non-accidental deaths in a witnessed seizure
- sudden unexpected deaths
- deaths related to status epilepticus
- accidental deaths as a consequence of seizures
- deaths as a consequence of treatment of epilepsy.
- suicides
- respiratory deaths

1.1.7 Studies of Proportional Mortality

Death in epilepsy may be 1) apparently unrelated 2) related to underlying disease, or 3) related directly or indirect to epilepsy as outlined in table 3. There is overlap between the three categories and cases need to be judged individually although it is not always possible to assign a death appropriately. Clearly not all accidents, suicides, sudden deaths or pneumonias are epilepsy-related. Similarly, most deaths from status epilepticus in hospital series, have been judged to be related to underlying disease (Oxbury & Whitty 1971). However, the presence of status may influence mortality related to the underlying condition as found by Goulon in bacterial meningitis where mortality was 82% in cases complicated by status compared with 33% without (Shorvon 1994).

Both population-based studies and those with known deaths (table 2) as their starting point provide data on proportional mortality. Wannamaker (1990) quotes different studies with deaths attributed to epilepsy accounting for 24% to 62% of the total although some of these exclude deaths due to tumour or cerebrovascular disease.

1.1.7.1 Accidental Deaths

Drowning

Drowning is a danger for the patient with epilepsy. Diekema

et al (1993) observed a relative risk of drowning for children (0-19) with epilepsy compared to those without of 13.8 (95% CI 7.0-27) and a relative risk of drowning in the bathtub of 96 (95% CI 33-275). Patients with epilepsy constitute some 0-8% of drowning series (Diekema et al 1993, Orlowski et al 1982, Ryan & Dowling 1993) and deaths from non-intentional drowning constitute 1.8-10% of deaths in epilepsy (Freytag & Lindenberg 1964, Iivanainen & Lehtinen 1979, Klenerman 93, Krohn 1963). Drowning may occur in the bath or while swimming but also if a seizure occurs by the waterside. The risk is greater in the absence of supervision and in association with other handicap. The relative risks of drowning in different circumstances have been addressed (Sonnen 1980), however, the merit of such comparisons is doubtful as differences are more likely to be exposure-dependant.

In 1991, in England and Wales there were 231 unintentional deaths by drowning (35 bath deaths) and a further 285 were unclassified as to whether they were accidental or purposefully inflicted (OPCS). How many of those had epilepsy is not stated. Although absolute numbers may not be large, their importance lies in the potential for prevention. Showering while seated with good ventilation and thermostat controlled water temperature poses a much smaller risk than the bath (Ryan & Dowling 1993). Similarly, advice given to patients regarding heights is not usually extended to unprotected waterfronts where

patients with epilepsy would be well-advised to keep a safe distance. Personal flotation devices during supervised watersports and informed supervision while swimming are essential (Ryan & Dowling 1993).

Other Accidents

Epilepsy patients are usually advised to avoid situations where the occurrence of a seizure may be particularly dangerous. The magnitude of accidental mortality is unknown as epilepsy is often not recorded when death certificates are issued in seizure-related fatal accidents. According to Zielinski (1974) epilepsy was cited in only 43% of such accidents. In proportional mortality studies accidental deaths (excluding drowning) constitute 0.8% -18% of total deaths from epilepsy (Freytag & Lindenberg 1964, Iivanainen & Lehtinen 1979, Klenerman 93, Krohn 1963). Other studies do not separate drowning cases (Hauser et al 1980, Henriksen et al 1970) while some (Zielinski 1974, Hashimoto 1989) separate accidental fatalities due to seizures from those not due to seizures, a distinction not always possible to make.

In addition to circumstance-dependant fatalities such as those due to road traffic accidents or burns, seizures associated with falls have their own risk. They may result in potentially fatal head injuries, cervical trauma, or fractures of limbs. Russell-Jones & Shorvon (1989) addressed the risk of head injury associated with seizures

based on the number sustained relative to total recorded seizures among long term residents with epilepsy. 2.7% of all seizures (6.1% if associated with falling) resulted in head injury requiring medical attention, but only one in every 4208 seizures associated with falls resulted in skull fracture, extradural or subdural haemorrhage. They concluded that while minor seizure related head injury was common, severe head injury was rare. It is not clear how many seizures may have occurred with protective helmets worn or on soft surfaces. It is interesting that non-drowning accidents in a mortality study at the same centre only constituted 0.8% of total deaths (Klenerman et al 1993) emphasizing that accidental deaths in epilepsy are potentially preventable.

One specific area regulated by legislation is that of epilepsy and driving. Legislation first introduced in Britain in the 1930's was absolute barring altogether a person "suffering from epilepsy" from holding a driving licence (Taylor 1993). The law has relaxed over the years and currently requires a one-year seizure-free period. This is in marked contrast for example to legislation in the State of Wisconsin where only a 3-month seizure-free period is required. Hansotia & Broste (1991a&b) conclude on the basis of Wisconsin data that "drivers with epilepsy or diabetes mellitus have slightly increased risks of traffic accidents" and state their view that the increases in risk do not justify "further restrictions on driving

privileges". Yet according to Taylor (1989), driver-collapse accounts for approximately 4 per 1000 serious road traffic accidents of which some 50% are due to epilepsy. While the majority of such cases are undeclared, how many would have satisfied the British, or indeed the Wisconsin, guidelines is unknown.

1.1.7.2 Respiratory

The susceptibility of patients with epilepsy to respiratory infections was highlighted by Munson (1910), and confirmed by other reports (Krohn 1963, Iivananen & Lehtinen 1979). In Krohn's view (1963) such patients were not dying of pneumonia, but getting pneumonia because they were dying. Patients who are debilitated or have uncontrolled disease are more at risk and in more recent series tended to be elderly (Klenerman 1993). Aspiration during seizures, however, is another possible mechanism, although this has not been formally tested.

1.1.7.3 Status Epilepticus

Prognosis and outcome have recently been reviewed (Shorvon 1994). Although status epilepticus is more common in children, mortality is higher in adults and appears to have declined in recent hospital series (18% of total cases, 7% of children and 28% of adults in combined results from 12 case-series after 1970 - Shorvon 1994). In most cases death

is considered mainly due to underlying disease with some 2% of deaths being directly attributable to status. Population based data is not available, and most hospital series reported are from specialised centres. Whether higher death rates occur in patients without severe underlying pathology when treated in less specialised units is unknown, nor is the proportion with iatrogenic deaths. The contribution at the present time of antiepileptic drug withdrawal emphasized by Hunter in 1959 in precipitating status (Shorvon 1994) is unknown. It is worth noting however that status epilepticus was a significant cause of death in patients with epilepsy in the era prior to the development of modern antiepileptic therapy (see section 1.1.8.2, pages 47 - 55).

Status epilepticus in proportional mortality data is listed as the cause in some 10% or less of epilepsy deaths (Krohn 1963, Zielinski 1974, Iivanainen 1979). Klenerman (1993) reported 0.8% death from status in a recent study of institutionalised patients as compared to 11% in the same centre two decades previously. Prompt treatment of the serial seizures/pre-status stage was felt to be partly responsible for the decrease, although more accurate certification may also have contributed, as previous unwitnessed sudden deaths were more likely to be attributed to status. Munson (1910) reported that 59 deaths (10% of total) at the Craig Colony were due to status epilepticus, *"much fewer"* from *"status and series"* than in the earlier

years of the colony. He felt that these were *"conditions which permit no temporizing and must be stopped as soon as possible"*, a view strongly held today (Shorvon 1994).

1.1.7.4 Suicides

The subject of suicide and epilepsy has been reviewed by Barraclough (1987) and Mathews & Barabas (1981) with both self-poisoning and suicides apparently increased in patients with epilepsy. In proportional mortality series suicides have constituted some 2-10% of total deaths. An exceptionally high 20% was reported from Denmark (Henriksen 1970) where suicide rates in general are particularly high (Dolley 1994). Suicide however was not reported to be increased in the population-based Rochester study with only 3 suicides reported in 8233 person-years. Zielinski reported a higher incidence among patients with epilepsy in the community as compared to institutionalised patients. An increased number of suicides has also been reported in post-temporal lobectomy patients particularly in the first few years after follow-up (Taylor & Marsh 1977). Force et al (1989) found a younger age at suicide than in the general population and an association with more severe epilepsy. Mendez & Doss (1992) partly on the basis of their experience with 4 patients suggest a greater association with psychotic behaviours and psychic symptoms than with major depression or the psychosocial burden of being epileptic. This would appear to be supported by the

observation that the excess risk has been estimated at 25 times that of the general population for patients with temporal lobe epilepsy (Barraclough 1987). While it may be that only selected groups are at particular risk early after diagnosis, this is clearly another area where deaths are potentially preventable.

1.1.7.5 Treatment Related Mortality

Cancer & Antiepileptic Therapy

It has been suggested that some antiepileptic drugs are associated with a small increased long-term risk of secondary neoplasia. Possible associations between phenytoin and lymphomas, barbiturates and liver tumours, and barbiturates and lung cancer have been addressed (Anthony 1970, Friedman 1981, White et al 1979). Excess lung cancer was reported in more than one study either within the first few years of diagnosis (Shirts et al 1986) or where smoking history was not available (Klenerman 1993). An excess of pancreatic and hepatobiliary (carcinoma of the gall bladder and cholangiocarcinoma) has also been reported (Klenerman et al) but numbers were small. In a study of over 2000 residents with epilepsy, White et al (1979) defined the limits of an overall increase in risk for cancer (excluding CNS) at between 1.1-1.8 times the average. Clemmesen et al (1974) and Shirts et al (1986) found no such overall increase. A recent large study of patients with epilepsy from Denmark (Olsen et al 1989)

showed no overall increased risk when brain cancers were excluded, a significant decrease in bladder cancer and melanomas, a non-significant increase of non-Hodgkins lymphomas, and a significant but small increase in lung cancers (relative risk 1.4, 95% CI 1.2-1.7). The lack of associated increase in bladder cancer did not support the hypothesis that the increase was smoking related.

In summary, once central nervous system neoplasms are excluded, any excess reported is small or borderline although doubt remains regarding neoplasms of the lung and non-Hodgkins lymphomas. At present these findings do not influence clinical decisions.

Deaths & Antiepileptic Therapy

Deaths may sometime occur as a direct consequence of an adverse reaction to antiepileptic therapy. Idiosyncratic reactions such as blood dyscrasia may be life-threatening. Hepatic failure fatalities with phenytoin, phenobarbitone and sodium valproate for example have been well-documented. In the case of valproate (Dreifus et al), such fatalities were most likely to occur in children with neurodeficit aged 0-2 years on polytherapy. Other examples include sinus arrest with carbamazepine (Jacome 1987, Stone & Lange 1986) and liver failure as part of an allergic reaction with lamotrigine (Duncan 1994). More recently, Felbamate has been associated with both liver failure and aplastic

anaemia. Comparative estimates of rates of occurrence of such deaths per treatment years are not available, and it is difficult to quantify the magnitude of risk. Accidental overdose of antiepileptic medication may also occur.

Mortality & Epilepsy Surgery

It may be expected that mortality after surgery for epilepsy would decline towards that of the normal population. However, as reported by Polkey (1989), whereas low peroperative mortality has continued to decline, long term mortality after surgery is elevated. Two series (Jensen 1975, Taylor & Marsh 1977) quoted report excess long-term mortality with some half to two-thirds of deaths related to seizures or suicides. Although as concluded by Jensen this may be less than expected in a non-operated group (a proposition not directly tested) it remains above that of the general population, and is thus a cause for concern.

1.1.8 Non-Accidental Seizure & Sudden Deaths (SUDEP)

1.1.8.1 Overview of Current Literature

Seizure related and sudden unexpected deaths in epilepsy were well-documented by medical attendants at residential institutions for patients with epilepsy (Bacon 1868, Munson 1910, Spratling 1904) . Currently they are familiar to both pathologists and coroners (Freytag 1964, Hirsch & Martin 1971, Leestma et al 1985) as well as at long-stay units (Klenerman et al 1993, Brown 1992). Yet they remain generally under-recognised, and indeed until recently the message has been that short of an accident consequent to a seizure epilepsy cannot be fatal. The general lack of awareness has meant that bereaved relatives have felt particularly isolated in their unexplained loss and only recently has a self-help group been formed in Britain (Epilepsy Bereaved? PO Box 1777, Bournemouth BH5 1YR).

The subject has been reviewed by Jay & Leestma in 1981 and a recent textbook has been dedicated to the subject (Lathers & Schraeder 1990). In such deaths post-mortem examination fails to reveal an anatomical or toxicological cause. Some witnessed deaths occur during or shortly after a seizure and a few occur with no clear convulsive movements. The majority however are unwitnessed and the person is usually found dead often in or off the bed. Evidence for an associated seizure is found in some 50% of

cases (Leestma et al 1989), and a past history of generalised tonic clonic seizures is reported in most (Birnbach et al 1991, Earnest et al 1992, Leestma et al 1989). Male Afro-Americans with excess alcohol intake have been reported to be more at risk (Leestma et al 1989).

In proportional mortality series between 7.5%-17% of deaths in people who have epilepsy fall into this category (Wannamaker 1990). These deaths occur whether seizures are moderately or poorly controlled although cohorts with more severe epilepsy appear to be at higher risk. The influence of epilepsy diagnosis as opposed to seizure type and frequency is still uncertain, but it has been suggested that sudden deaths are more likely in remote symptomatic epilepsy, with a higher percentage of anatomical lesions found on neuropathology than in epilepsy patients dying in other circumstances (Leestma 1990). It has also been suggested, on the basis of post-mortem antiepileptic drug levels, that withdrawal/noncompliance may be a precipitating factor (Bowerman et al 1978, Lund & Gormsen 1985). Apart from the questionable reliability of post-mortem samples (Brown et al 1990), the value of drug levels, once overdose is excluded, is open to debate as 'subtherapeutic levels' are adequate for many patients. Furthermore sudden unexpected death in epilepsy was recorded (Munson 1910) before the introduction of modern antiepileptic therapy. Nevertheless, the potential contribution of improved seizure control in reducing risk

of sudden death, and the dangers inherent in noncompliance and drug withdrawal should not be dismissed. Comparisons of incidence in treated and untreated population based-cohorts are not available.

Incidence of sudden death in a general population with epilepsy has been estimated at between 1:370 and 1:1,110/yr (Leestma 1989). Jick et al (1992) reported an estimated incidence of 1.3/1000 years at risk among individuals aged 15-49 years. Certain selected populations however have a much higher risk. 7 out of 151 cases over a five-year period were reported among patients enrolled in an adult epilepsy surgery programme (Dasheiff 1991). An incidence of 1:260/year was reported for combined sudden unexpected and seizure-related deaths among long-term residents with epilepsy (Klenerman et al 1993). At the other end of the spectrum, in terms of frequency of seizures, only 2 such deaths were reported by the Medical Research Council Antiepileptic Drug Withdrawal Study Group (1991 & 1993) involving 1013 patients and up to 5 years follow-up.

In the Cook County Series of 60 cases (Leestma et al 1989) mean age at death was 35 years. This is consistent with other studies suggesting that young adults are at increased risk. Information on other age-groups is limited. Such deaths in an elderly population are difficult to separate from deaths due to ischaemic heart disease. However Luhdorf et al (1987) found a higher incidence of sudden death in

general than expected in an elderly population with epilepsy. Annegers et al (1984), based on mortality findings in an unselected population with epilepsy, reported an excess of ischaemic heart disease in persons under 65. However 13/48 "cardiac deaths" at all ages were sudden in previously healthy individuals, 8 in the remote symptomatic group, 4 the idiopathic group and 1 the neurodeficit group. The increased SMR's reached statistical significance only in the remote symptomatic group, the other numbers being too small to exclude an increased risk. Ages and post-mortem findings were not detailed but all sudden deaths were attributed to ischaemic heart disease. There were three mutually exclusive categories depending on presentation. SMR was highest for the sudden death group at 2.29 (95% CI 1.22-3.93), intermediate for myocardial infarction and comparable to the general population for angina pectoris. Furthermore 5.5% (13) of deaths in the study were directly attributed to epilepsy (details not supplied). Given close to 10,000 person years and an approximate incidence of 1:1000 of sudden death (unrelated to IHD) in an unselected community-based cohort, 10 such cases only may be expected. This data may not therefore be at variance with other sources.

Sudden deaths in epilepsy do occur in children and constituted in one study 10% of total sudden deaths among children aged 2-20 years (Keeling and Knowles 1989). In another study, 11/93 deaths among children with epilepsy

were probable "sudden unexplained deaths" (Harvey et al 1991). In a clinical series, 3 of 120 children with epilepsy and no neurological deficit followed up for up to 12 years (total years of follow-up not stated) died a sudden unexpected death (Brorson & Wranne 1987). It remains uncertain although possible that incidence is lower in children than in young adults, and that children with mental handicap and/or neurological deficit may be at an increased risk.

Causes of deaths stated in death certificates in such cases (Lip & Brodie 1992) vary and include status epilepticus, epileptic seizure, asphyxia, anoxia, respiratory arrest, suffocation, and unascertained. Except where they occur in residential institutions or in hospitals they are likely, in Britain, to be referred to the coroner and thus circumstances of death are recorded.

Pulmonary oedema, well documented in seizures, with or without congestion of other organs is a frequent post-mortem finding in sudden death cases (Leestma et al 1989, Terrence et al 1981). Mechanisms put forward have recently concentrated on the possible role of cardiac arrhythmias as the primary event. Although changes in cardiac rate are common (Blumhardt et al 1986), malignant arrhythmias appear to be relatively rare in seizures. They are however reported as case-reports and include bradycardia and sinus arrest (Joske & Davis 1991, Fincham et al 1992). Hypoxia

secondary to central or obstructive apnoea or pulmonary oedema is an alternative hypothesis. Changes in respiratory pattern including apnoea occur during seizures (Schraeder & Lathers 1990). Both cardiac and respiratory disturbances or other as yet unknown mechanisms may play a part. The release of endogenous opioids peri-ictally (Ramabadran & Bansinath 1990), for example, may aggravate autonomic disturbances already present. It has been suggested that cases where no clear convulsive movements occur the deaths may still be in the context of a paroxysmal epileptiform EEG discharge (Brown 1992). Reported autonomic changes during seizures are further addressed in section 1.2.2 (pages 66 - 70).

The question has arisen as to whether suffocation due to external factors plays an important role as argued by Wilson (1973 & 1978) who advocated smother-proof pillows (section 3.1.2.3, page 87) given the nocturnal nature of many of these deaths. The David Lewis Centre, Cheschire, however have not observed a change in sudden death incidence on changing over to such pillows (Brown S W 1994, personal communication).

1.1.8.2 Sudden Deaths Prior to Modern Antiepileptic Therapy

The question of whether specific modern antiepileptic agents predispose to sudden death sometimes arises. Apart from rare instances of sinus arrest in the case of carbamazepine (section 1.1.7.5, page 39), evidence in support of this view is lacking. Within this context, it would be useful to review earlier physicians' experience of mortality and sudden death in epilepsy in the era prior to modern antiepileptic therapy before phenobarbitone was introduced in 1912. Treatments available were of limited efficacy and physicians working is asylums had an unrivalled opportunity for direct and prolonged observation.

Definitions and the use of terminology in this field has varied over the years and indeed no consensus has yet been reached. Some writers (Delasiauve 1854) did not use the term sudden death, and assuming that many of these deaths were due to suffocation, grouped them with other accidental deaths. Others (Munson' 1910) on the other hand used the term sudden death in a broad sense that also included traumatic fatalities.

Delasiauve (Medicin des Alienes de L'Hospice de Bicetre - Section des Epileptiques et des Idiots) in his 'Treatise on Epilepsy' (1854) addressed outcome including mortality. He classified 52 deaths based on his personal experience and

that of other authors and described four categories - a) "fortuitous" seizure-related deaths (total 9) including 2 traumatic, 5 suffocation, 1 obstruction from food and 1 cardiac rupture, - b) deaths from serial seizures or status (total 13), - c) deaths from apoplexy or meningism (total 15), and - d) unrelated deaths (total 15) including among others pulmonary deaths. It is therefore possible to distinguish in Delasiauve's writing a) *single-seizure deaths of diverse mechanisms*, those due to b) *status epilepticus*, those likely to be due to c) *underlying disease* and deaths from *d) other causes*. It is worth noting that he reported more serial seizures/status deaths than single-seizure deaths from all causes.

After addressing traumatic seizure-related deaths in previously otherwise healthy patients with epilepsy he stated that death is often due to mechanical suffocation:

"Affected by seizures in bed, the patients instinctively turn over onto their abdomen. The paroxysm catches them in this position and nails them, somehow, against the pillows or the bolster. The interruption of air, in the absence of help, is quick to cause asphyxia. One records therefore the violaceous swelling of the face, the neck and sometimes the upper chest, the flattening of the lips stuck to the tongue which protrudes at their opening, the crushed nostrils and

different signs of cerebral and pulmonary congestion."[2]

Reference has already been made to G Mackenzie Bacon's article in the Lancet (1868) entitled "On the Modes of Death in Epilepsy" which was based on his experience as Medical Superintendent of the Cambridge County Asylum. 3354 patients with incurable epilepsy were in public asylums in England and Wales in 1867. Prevalence of epilepsy at that time was estimated at 1.5 per 1,000 of the general population (Lord 1899) although this figure excluded *"insane epileptics"*. Bacon clearly made a distinction between primary and secondary epilepsy although he predicted that primary cases would be reduced by more precise knowledge of causes. He did not address deaths due to underlying disease or to unrelated causes and concentrated on deaths related to the epilepsy itself. He clearly differentiated as already stated between deaths *"arising from the long continued effects of the disease on the body"*, those after *"a rapid succession of fits"*, *"Sudden deaths in a fit"* and *"Accidents due to fits"*.

While stating that deaths in a fit were more rare (than after a series of fits) he described some of the causes of death in a fit which include *"asphyxia"* (violence of the spasm with venous congestion), *"loss of nervous power"* (heart or its nerves) and *"suffocation"* (face buried in

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[2]My translation

something soft, impaction of food, aspiration etc..). He stated that of the causes enumerated suffocation in bed was *"far from uncommon in asylums"*.

He therefore described non-traumatic deaths from single seizures occurring both with and without an extrinsic mechanism.

Geysen (1895) at the age of 22 submitted a thesis on the subject entitled " De La Mort Inopinee ou Rapide Chez les Epileptiques". He drew widely from literature current at the time quoting numerous case-reports. He stressed that death from status epilepticus was more common than from a single seizure. The latter in his view was much less likely to occur from asphyxia due to the violence of the seizure itself in the absence of suffocation or pre-existing disease. In his view it was more likely to occur if the individual was already compromised (e.g. had pulmonary or cardiovascular disease), or in the presence of concomitant circumstances such as suffocation, drowning, burns or other injury.

Geysen also quoted data presented in 1865 by Rengade & Reynaud who looked at "accidents" due to epileptic seizures based on 316 individuals with epilepsy over a six year period. During this period 4 nocturnal deaths were felt to be due to suffocation: a minimum unexpected sudden death rate of 1:474 person years, a figure likely to

significantly underestimate the overall non-traumatic non-drowning single seizure death rate in that setting as it includes only those nocturnal deaths where suffocation was thought likely.

Gowers (1885) also addressed prognosis in epilepsy under three headings *1) The danger to life; 2) The prospect of a spontaneous termination...; 3) The prospect that by treatment the disease may be a) cured, or b) the attacks arrested.*

Only two short pages were devoted to the subject of mortality in his textbook on epilepsy. He stated that *"The danger to life in epilepsy is not great". "Alarming as is the aspect of a severe epileptic fit....., it is extremely rare for a patient to die during a fit. The chief danger of death in an attack is the liability to accidental asphyxia, in consequence of the occurrence of an attack during a meal, when food may get into the air-passages, or of vomiting during an attack with the same result, or in consequence of the patient, in bed, after an attack, turning on to the face and being suffocated in the post-epileptic insensibility".* He went on to say that there was *"some risk of death by other forms of accident to which the attacks expose the patient"* such as burns and drowning and that *"the commonest mode of accidental death in epilepsy is by drowning".*

He considered the danger of *"accidental death"* to be *"unquestionably greater than that of death from the direct severity of a fit"*. He acknowledged *"status epilepticus"* to be *"a state of considerable danger; it is, however, so rare, and the liability to it is so small, that it cannot be regarded as measurably increasing the risk of death in consequence of the disease."*

Although Gowers view that many deaths from epilepsy were accidental, including cases that would be included under the category of "Sudden Death" today, was in agreement with other writers of his time, his assessment of the magnitude of risk appears to differ from that of others in terms of seizure-related deaths in general, and more specifically, deaths from status epilepticus. Unlike his chapters on other aspects of epilepsy where he draws on his experience of 1450 cases with epileptic and "hysteroid" attacks, which were amply furnished with case histories, tables and numbers, his conclusions on mortality were remarkably devoid of detail nor did he state whether his conclusion were based on current literature or personal experience of deaths in epilepsy.

One can only speculate about the reasons for the apparent difference in his assessment from that of other writers. It may be that outcome in outpatients may not have been known or that his patients may have had less severe epilepsy. The lack of data to support his views at a time when both he

and other writers liberally used detailed figures is surprising.

The discrepancy between Gowers' viewpoint that the danger to life from epilepsy was not great and that of others was noted by Spratling (1904) in his textbook on epilepsy. Spratling's interpretation of the different views reflects a difference in outlook between expectations then and now. He reflects that "...*a disease which destroys life suddenly and without warning through a single, brief attack, unaided by an accident to the patient at the moment, such as suffocation or fracture of the skull from falling, and does so in from 3 to 4 per cent. of all who suffer from it ...*" may not be considered of "excessively high mortality". However, if deaths in epilepsy from additional causes were considered it becomes a *"serious affection"*.

Thus, in contrast, Spratling and later Munson (1910), based on their experience at the Craig Colony were in no doubt that epilepsy constituted a risk to life.

Spratling (1902) summarised his data as follows: *"Out of every 100 epileptics who die about 4 do so as the result of a single fit: about 24 as a result of status epileptics: about 12 as a result of some accident, including suffocation in bed; about 24 as a result of some disease of the lungs, chiefly tuberculosis: about 10 as a result of some organic disease of the heart; and about 26 from all*

other causes".

It is again interesting that status deaths were reported as relatively common and that some 40 deaths out of each hundred were epilepsy related. Again nocturnal deaths are listed as accidental, and Spratling's view was that in patients with nocturnal seizures who habitually rolled over on to their front *"many would have unquestionably perished had they not received prompt attention from the nurse in charge"*.

A more detailed and later account of death in epilepsy at the Craig Colony was given by Munson in 1910 in which he reports on 582 deaths among 2732 individuals, with 50% of the deaths occurring between the ages of 15 an 29 inclusive (mean age of death 30.8 years). He found *"the proportion of males and females dying to be practically the proportion of those admitted"*, though the males were *"very slightly in excess"*. Mean duration of epilepsy was 17.58 years. Within the category of sudden deaths of which there were 99 cases (*"at the basis of all was a seizure"*), he included status and serial cases, suffocation and other accidents, and *"a definite and fairly large group where neither accident of any kind nor suffocation can be assigned as the cause of death"* which seemed *"to be intrinsic rather than extrinsic"*.

Munson highlighted various issues worth noting. He

considered the patient with epilepsy at particular risk of various pulmonary conditions frequently represented in his series. He emphasized pulmonary oedema *"a frequent and dangerous condition following all forms of the epileptic attack, even single grand mal seizures"*. He noted as previously mentioned *"fewer deaths from status and series"* than in earlier years at the Colony, conditions that he considered permitted *"no temporizing and must be stopped as soon as possible"*. He noted on the other hand that the category of sudden death had shown no diminution and discussed possibilities if any of prevention. He concluded that *"death is imminent at the time of seizures, unless help is at hand. The cause may be traumatic, suffocation may take place, or death may occur without any apparent cause... The moral....(being that) the epileptic should be by himself as little as possible"*.

In summary, epileptologists at the turn of the century were well aware of the dangers from seizures and recognised that seizure-deaths could be accidental (a category that included trauma, burns, drowning, suffocation or aspiration) or due to intrinsic mechanisms in a single or serial seizures/status, the latter being the more common. Their wide experience was based on direct observations at colonies. While these must be regarded as selected cohorts, they represent experience prior to modern antiepileptic therapy, and at a time when perhaps a larger proportion of all patients with epilepsy resided in institutions.

1.2 Physiological Changes During Seizures

Transient or early (0-30 minutes) changes that occur during generalised seizures are listed in table 4 (Meldrum 1988). These may be a consequence of either the motor component of a seizure, or of autonomic and endocrine changes secondary to neuronal discharges as shown when seizures are recorded in paralysed animals.

Table 4: Early Physiological Changes During Seizures

Arterial hypertension
Cerebral venous pressure raised
Arterial PO2 low or normal
Arterial PCO2 high
Central venous PO2 normal (or low or high)
Central venous PCO2 high
Cerebral blood flow increased
Hyperglycaemia
Hyperkalaemia
Haemoconcentration
Lactacidosis

Adapted from Meldrum 1988

Various mechanisms account for these different changes. Raised cerebral venous pressure for example is thought to be mainly due to the motor component occurring particularly during the tonic phase and in whole body jerks. It is also partly due to cerebral vasodilation as it is also raised in paralysed animals. Arterial PCO2 rises due to a decrease in gas exchange and increase in metabolism. Central venous PO2 varies as excess demand may be more than compensated for. Hyperglycaemia is thought to be secondary to adrenaline which results in the release of glucagon. In adrenalectomised rats with induced seizures hypoglycaemia rather than hyperglycaemia occurs via insulin release which can be blocked by vagotomy. Haemoconcentration is due to release of splenic red cells coupled with excess secretions.

Cardiovascular changes occurring commonly in seizures, whether spontaneous, ECT or drug-induced, include tachycardia and hypertension. These are abolished by ganglionic blockade and by spinal section, and are thought to be initially sympathetically mediated and later maintained by motor activity. A marked early rise in cerebral blood flow which may be focal or generalised occurs within seconds. This is due to increase in blood pressure and to cerebral vasodilation. The latter is probably neuronally mediated in the first instance, but is maintained by increased metabolic demands with increase in PCO2 and lactic acid and decrease in PH. These changes

accompany an increase in oxygen consumption ratio demonstrated in animals.

Many factors contribute to the occurrence of hypoxia and hypercapnia; these consist of changes in central regulation of respiration, increased demand due to motor activity, mechanical impairment of ventilation as well as autonomic changes which include excessive bronchial secretions, pulmonary oedema and bronchial constriction.

Table 5: Sympathetic & Parasympathetic Effects

Sympathetic	Parasympathetic
Tachycardia	Bradycardia
Arterial Hypertension	Cerebral Vasodilation
Skin Vasoconstriction	Bronchial Constriction
	Exocrine Secretion
Mydriasis	Miosis
Galvanic skin response	Bladder Contraction
Sweating	
Adrenaline release	
Glucagon release	

Adapted from Meldrum 1988

Although autonomic changes are often emphasized in partial seizures they are even more a feature of generalised seizures. They have also been shown to occur to a lesser extent in absence seizures. They reflect both overactivity of the sympathetic and parasympathetic systems (table 5). These changes are thought to be mediated via the amygdala and hippocampus and hypothalamic connections to other centres.

Endocrine changes such as increased plasma prolactin, ACTH and cortisol, sometimes used to differentiate between seizures and pseudoseizures in the case of prolactin, are also mediated through the limbic system and hypothalamic control over the pituitary.

1.2.1 Basic Physiology

1.2.1.1 Control of Ventilation

Breathing is automatic; its periodic nature is controlled by the brainstem; it may be modified by input from the limbic system and hypothalamus as well as by voluntary control. The following account summarises control of ventilation as described by West (1985).

Central control involves three groups of nuclei:

- Medullary Respiratory Centre
- Apneustic Centre (lower pons)
- Pneumotaxic Centre (upper pons)

The medullary respiratory centre is within the reticular formation of the medulla and consists of a dorsal respiratory group associated with inspiration and a ventral respiratory group associated with expiration. In normal quiet breathing inspiration is active and expiration passive. One view holds that it is the inspiratory area that has the property of intrinsic periodic firing. Output from the inspiratory centre is inhibited by the pneumotaxic centre, thus shortening the inspiratory phase of the cycle and increasing respiratory rate. It is also modulated by impulses from the vagal and glossopharyngeal nerves which terminate in the closely situated tractus solitaris.

Impulses from the apneustic centre apparently have an excitatory effect on the inspiratory centre such that sections just above that site result in prolonged inspiratory gasps (apneuses).

The muscles of respiration, the diaphragm, intercostal, abdominal and accessory muscles work in a coordinated fashion under central control. A feedback system operates

which is mainly dependent on the following sensors:

- Central Chemoreceptors
- Peripheral Chemoreceptors
- Lung Receptors
- Other receptors (baroreceptors, joint, muscle, upper airway...)

Hypercapnoeic ventilatory drive in mainly dependent on central chemoreceptors. These are located near the ventral surface of the medulla, respond to changes in H+ concentration and are therefore involved in the minute-by-minute control of ventilation. Since CO2 diffuses across the blood brain barrier, a rise in blood CO2 is reflected in a decrease in CSF PH which stimulates ventilation. Compensation does occur however with transport of HCO_3^- across the blood brain barrier whereby patients with long-standing CO2 retention having a nearly normal CSF PH.

Hypoxic ventilatory drive on the other hand is dependent on the carotid (and aortic) bodies. These have a very rapid response with an increased discharge rate with decreased arterial PO2, increased PCO2 or decreased PH (carotid body only).

Lung receptors include pulmonary stretch receptors with impulses travelling via the vagus and showing little adaptation. Inflation of the lungs inhibits further

inspiratory muscle activity (Hering-Breuer inflation reflex) and deflation initiates inspiratory activity. These reflexes are largely inactive in adults. Other lung receptors include irritant receptors and juxta-capillary receptors.

Other receptors include arterial baroreceptors whereby an increase in blood pressure can stimulate the carotid and aortic sinus baroreceptors and cause reflex hypoventilation or apnoea. The converse is also true but the pathways for these reflexes are largely unknown.

Under normal conditions control of ventilation depends on PCO2 which is maintained to within 3 mm Hg. PO2 on the other hand may drop to 50 m Hg (if PCO2 is maintained) without any appreciable change in ventilation occurring.

1.2.1.2 Control of Cardiac Rate

Control of cardiac rate is mediated by sympathetic and parasympathetic pathways (Spyer 1992).

Spinal sympathetic preganglionic neurones are innervated by descending pathways from hypothalamic, midbrain, pontine and medullary cell groups. Chronotropic sympathetic neurones are restricted to the upper thoracic cord (T1-T4) in the intermediolateral cell column. Cardiac sympathetic

fibres emerge from spinal cord on either side and synapse in sympathetic ganglia then go on to the cardiac plexus. Sympathetic stimulation increases nodal firing rate, conduction rate and ventricular force. A clear relationship has been demonstrated between the rate of firing of some of the excitatory bulbospinal projections and changes in blood pressure, increase in firing being associated with decrease in blood pressure and vice versa. Heightened activity has also been demonstrated during inspiration.

Parasympathetic cardiac chronotropic fibres are carried by the vagus nerve having originated in cardioinhibitory cells of the nucleus ambiguus in the medulla. The nucleus ambiguus receives input from the forebrain, hypothalamus, amygdala and lower brainstem including the nucleus of the tractus solitarius. After leaving the vagus the fibres synapse in the cardiac plexus and in ganglia; postganglionic fibres from the right vagus supply the sinoatrial node and atria, and those from the left vagus the conducting tissue and ventricular myocardium. These are muscarinic.

The nucleus of the tractus solitarius receives afferents from arterial baroreceptors, arterial chemoreceptors and respiratory receptors. It is therefore considered a potential site for interaction of the cardiovascular and respiratory systems, with connections with the nucleus ambiguus (parasympathetic) and the ventrolateral medulla

(sympathetic 'vasomotor centre').

1.2.1.3 Cardiorespiratory Reflexes

A complex interaction exists between the regulation of the cardiac and respiratory systems (Spyer 1992). Cardiorespiratory reflexes constitute part of the battery of clinical tests used in suspected autonomic dysfunction, for example heart rate response to deep breathing and the Valsalva manoeuvre. Sinus arrhythmia for example is known to be the consequence of the respiratory control of the vagal outflow of the heart. Tachycardia occurs on inspiration with suppression of preganglionic vagal neurones. One reflex of particular interest in this context is that of bradycardia occurring in the presence of apnoea. Daly (1985) has emphasized 'the risk of cardiac arrest' 'in any clinical situation in which the patient's respiration is depressed either reflexly or centrally' 'if an excitatory input to the cardiac vagal motoneurones is elicited'. Such an input may occur as a direct consequence of apnoea via carotid body chemoreceptors. In humans the primary cardiac response from stimulation of the carotid bodies is bradycardia. In the presence of spontaneous breathing this is usually overridden by other mechanisms with tachycardia occurring secondary to reflex hyperventilation. In the presence of apnoea, however, hypoxia is more likely to result in bradycardia (Daly 1986). Spyer (1992) considered that any input that produces

a period of apnoea may be regarded as a time when potentially fatal bradycardias may be induced with heightened sensitivity of vagal motoneurones.

Heart rate responses in clinical autonomic testing (inspiration/expiration, Valsalva and response to standing) have been shown to be age-dependent with a steady decline in variability with age (Wieling 1992 - Figure 1).

Figure 1: Forced Breathing & the Valsalva Manoeuvre

Age (years)	I-E difference* (beats/min)	Valsalva ratio†
10–14	<17	<1.53
15–19	<16	<1.48
20–24	<15	<1.43
25–29	<14	<1.38
30–34	<13	<1.33
35–39	<12	<1.28
40–44	<11	<1.24
45–49	<11	<1.20
50–55	<10	<1.16
55–60	< 9	<1.12
60–65	< 9	<1.08
65–70	< 8	<1.04
70–75	< 7	<1.00
75–80	< 7	—

*Abnormally low scores for I-E difference are defined as scores below $P_{0.025}$.
†Abnormally low values for heart rate changes induced by the Valsalva manoeuvre are expressed as the Valsalva ratio.

Reproduced from Wieling 1992

1.2.2 Electrocardiography During Seizures

Case reports describe the occurrence of bradycardia and sinus arrest as part of the manifestations of epileptic seizures (Katz et al 1983, Joske & Davis 1991). Joske & Davis reported one case and reviewed 8 others. Loss of consciousness may be ictal or reflect impaired cerebral perfusion (Fincham et al 1992, Jacome 1993). Most cases were considered temporal in origin and could occur with either side being involved. Respiratory parameters during these seizures are not commented on in these adult cases. Apnoea and bradycardia in an infant with partial seizures was documented by Coulter (1984) and a clear bradycardia occurring after apnoea was demonstrated by Lugaresi et al (1986) in a case of nocturnal paroxysmal bradycardia a condition considered since to be epileptic in nature.

More systematic studies of autonomic changes have been undertaken by a number of workers and have been comprehensively reviewed by Jallon (1991).

Mosier et al (1957) premedicated patients with atropine who were then paralysed using a succinylcholine infusion and ventilated with 100% O2 and positive pressure. The block excluded one foot with the use of an inflated blood pressure cuff above the ankle. Seizures were then induced using Metrazol. Blood pressure, EEG, ECG and EMG were recorded. Patients remained conscious until the seizure

occurred. They studied 41 patients (17f, 24m), 5 with "idiopathic grand mal", 19 "psychomotor" and 15 "focal convulsive" epilepsy and 2 with nonepileptic attacks. Duration of seizures recorded ranged from 1 to 63 minutes with the majority less than 5 minutes. Their results confirmed a sudden rise in blood pressure and pulse rate, and showed evidence of arrhythmias in 9 of 41 patients. This occurred during the clonic phase, and consisted of atrial and ventricular premature contractions, runs of bigeminy, ventricular tachycardia (including bidirectional ventricular tachycardia). Changes in such seizures however cannot be assumed to be representative of seizures occurring spontaneously particularly that patients were premedicated with atropine with regular ventilation with 100% oxygen maintained. These factors would lessen the likelihood of bradycardia occurring.

Blumhardt et al (1986) recorded 74 spontaneous seizures in 26 of 50 consecutive cases with a history of temporal lobe epileptic seizures, in 12 before treatment. They included 15 male and 11 female patients with a mean age of 33 (range 14-75). Twenty had "idiopathic" epilepsy, 6 had a history of head injury or encephalitis, 2 had known tumours and two cerebral infarction. Nine had a history of TCS and none had a history of cardiac disease. Four channel recordings were undertaken (2 EEG: T3/P3 T4/P4, 1 ECG, 1 marker). The results showed an increase in heart rate in 24/26 patients, which in 67% of seizures reached more than 120 beats per

minute (bpm) and in 12% more than 160. They also reported significantly greater acceleration in younger patients and those off treatment. Only one patient had "*considerable*" slowing of heart rate in each seizure. A period of instability consisting of accelerations and decelerations at the end of seizures was noted. One patient had an ictal supraventricular tachycardia which also occurred interictally. The same changes occurred when more than one seizure was recorded in the same patient. This study seemed to indicate that ictal tachycardias were very common but bradycardias relatively rare in this type of patient.

Keilson et al (1989) also studied electrocardiographicy changes during 106 electrographic seizures (41 lateralised and 65 generalised) of at least 30 seconds in 45 patients using an 8 channel ambulatory EEG and excluding those with EEG changes of 3Hz spike and wave. They reported that 96% had an increase in heart rate, which in 48% greater than 150bpm. Again asystole and bradycardia were not found.

In another study (Nousiainen et al 1989) 3 patients with CPS (11 attacks) and 10 patients with psychogenic seizures (47 attacks) were compared. Mean rise of 62 bpm was recorded in the first group compared to only 9 bpm in the second with a quicker return to normal. One patient had a drop from 150 bpm to 40-45 bpm followed by extrasystoles or atrial fibrillation at the onset of seizures.

Other authors have looked at "cardiac" patients presenting with " *Atypical anginal pain and visceral symptoms*" who turn out to have epilepsy. Of 6 such patients described by Devinsky (1986) one had sinus tachycardia and the other bradycardia with syncope.

In this context it is worth drawing attention to Wilson's article on "Epileptic Variants" which includes visceral presentations along with a comprehensive and observant account of the range of presentations of epileptic attacks (1928).

In summary, systematic studies of seizures according to current literature indicates that while tachycardias are very common, bradycardia/sinus arrest are rare. Keilson et al (1989) concluded that identification of those at risk of sudden unexpected death may not be possible. Yet cases of ictal bradycardia and sinus arrest are reported. Are they as rare as the systematic studies suggest?

The question has arisen as to whether prolonged QT interval, a known risk factor for ventricular tachyarrhythmia, syncope and sudden death (Lancet 1991) may also be a risk factor in sudden deaths in epilepsy. This was recently addressed by Tavernor et al (1994) who retrospectively studied available ECG recordings in 10 sudden death cases. Corrected QT interval for heart rate (QTc) was within the accepted normal range for all ten

patients suggesting that prolonged QTc is not a major risk factor in SUDEP.

A recent study in rats showed that activation of both hypothalamic and mesencephalic neurones in the absence of any metabolic derangement caused bradyarrhythmic episodes which were more pronounced with simultaneous stimulation of both zones than with either alone. A clear neurogenic cardiovascular impairment was therefore demonstrated but not cardiac deaths suggesting that additional derangement, perhaps metabolic, during seizures may be necessary to cause death (Mameli 1993).

1.2.3 Apnoea

Apnoea is well known to occur in major seizures as described by Gowers (1885):

"At the onset of the severe fit the spasm is tonic in character... (and) involves the muscles of the chest and abdomen... the face usually at first pale, becomes suffused then livid, as the chest is fixed and respiratory movements are arrested...(and) cyanosis comes on... Presently, when the cyanosis has become intense, the fixed tetanic contractions of the muscles can be felt to be vibratory, and the vibrations increase to slight visible remissions. As these remissions become deeper, the muscular

contractions become more shock-like in character and the stage of clonic spasm is reached... In the resulting movement of the chest, air is expelled from the thorax and bloody saliva is frothed out between the lips. The air entering the lungs is at first insufficient to lessen the lividity, and the patient may seem to be at the point of death. But as the intervals between the shocks of spasms lengthen, and the remissions become greater, more breath enters the chest..."

Although undoubtedly common and frequently quoted as a feature of seizures systematic studies of apnoea are rare. Studies in infants are beyond the scope of this work, however, partial seizures presenting with life-threatening apnoea have been reported in infants (Singh et al 1993, Coulter 1984).

In a study of autonomic changes during paroxysmal EEG activity, Johnson & Davidoff (1964) studied 54 cases with idiopathic epilepsy with paroxysmal generalised EEG changes on a normal background with no focal signs on examination or focal EEG changes. These included EEG changes of 3 cycle/second spike and wave, other spike and wave, generalised spikes and slow-wave bursts. Modest autonomic changes were recorded, and included increase or decrease in heart rate and respiration. Prolonged apnoea (undefined) was noted in only 2/48 cases with spontaneous discharges. Discharges with clinical manifestations were more likely to

be associated with autonomic changes.

Van Buren & Ajmone-Marsan (1960) looked at the correlation of autonomic and EEG components in Metrazol (pentylenetetrazol) induced seizures. They studies 20 cases of temporal lobe epilepsy. Tachycardia and fall in skin resistance were very common, followed by oesophageal peristalsis, inhibition of respiration and hypertension. 6 had respiratory apnoea occurring in expiration, and this correlated with loss of consciousness. Bradycardia occurred in two cases.

Van Buren (1960) also looked at sensory, motor and autonomic effects of mesial temporal stimulation in man. He studied 11 patients two of whom had expiratory apnoea and one a reproducible bradycardia. The majority of responses to stimulation arose from within or very close to the amygdaloid nucleus and the pes hippocampus. Stimulation studies of the cingular gyrus in monkeys have also been shown to cause respiratory slowing and respiratory arrest in expiration as well as bradycardia and sinus arrest (Ward 1948). Such studies underline the involvement of the limbic system in neuronal cardiorespiratory control.

Nelson (1968) in an article entitled: Respiratory arrest from seizure discharges in limbic System" reported an apparently unique case with recurrent prolonged apnoeic attacks without evidence for associated convulsions that

were thought to be ictal in nature. Timely resuscitation suggested more than one near-miss sudden death event. The patient was considered to have temporal lobe epilepsy.

1.2.4 Pulmonary Oedema

Pulmonary oedema following generalised seizures is well documented (Bloom 67, Chang & Smith 1967, Greene et al 1975, Sarkar & Munshi 1977, Archibald & Armstrong 1978, Terrence et al 1980, Bonbrest 1964). It was emphasized by Munson (1910) Ohlmacher (1910) and Shanahan (1908) early this century.

Pulmonary oedema may be recurrent with generalised seizures, and has been radiologically proven. It can be differentiated from aspiration pneumonitis in not being associated with fever and in resolving both clinically and radiologically over a shorter time course. Its mechanism as discussed by Terrence et al (1980) is uncertain. Sympathetically mediated peripheral vasoconstriction, redistribution of vascular volume with pulmonary hypertension and pulmonary vasodilation with increased permeability have been suggested. It may be a variant of neurogenic pulmonary oedema. Of particular interest is the observation that the majority of case of sudden death are found to have pulmonary oedema at post-mortem. As Terrence states, this suggests that the lethal event in sudden death

cases is not instantaneous.

Olmacher observed that pulmonary oedema may 1) accompany *"a single major fit with death soon succeeding"* 2) occur *"after a single attack with coma, and death at a longer interval"* 3) occur *"after a series of fits not reaching status epilepticus"* 4) hasten *"status epilepticus to a lethal termination"*. Frequency of occurrence after single TCS is unknown.

1.2.5 Anoxia

Limited information is available regarding the occurrence of hypoxia during spontaneous seizures outside studies in infants. James et al (1991) reported a *"striking fall in oxygen saturation"* with an average reduction of 14.5% in 6/8 patients with TCS in the emergency room. It is difficult to define levels of oxygen saturation below which damage would ensue. The degree of anoxia that can be tolerated depends on many other variables in particular perfusion.

1.3 Ictal Cardiorespiratory Parameters - Noninvasive Measurement

1.3.1 Background

As has been indicated above limited data is available regarding respiratory changes during seizures and their relation to alterations in cardiac rhythm. It was felt that in the same way as is routinely performed in standard polysomnography (American Thoracic Society 1989), it should be both possible and informative to record non-invasively the same parameters during seizures, namely pulse oximetry, respiratory effort and airflow in addition to routine videotelemetry. While advances have taken place in the noninvasive measurement of blood pressure and transdermal CO2, both of which would also be of considerable interest during seizures, such advances were not considered sufficient at this stage to make ictal recording of these parameters feasible.

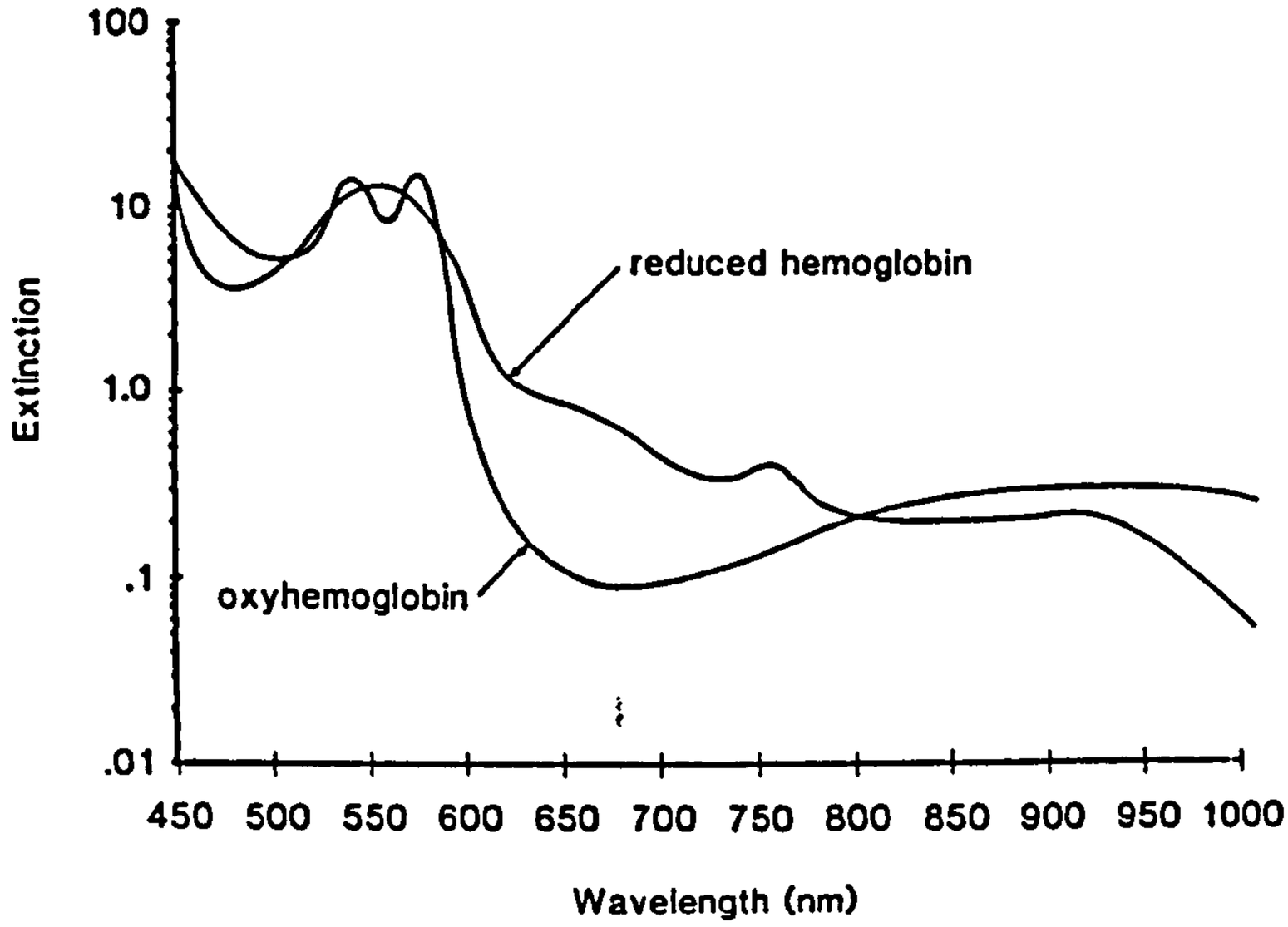
Although standard equipment is available for recording oximetry, respiratory effort and airflow, there are limitations to their use particularly where movement artefact may be expected.

1.3.2 Pulse Oximetry

1.3.2.1 Principles

Total arterial oxygen content is made up by the portion dissolved in plasma (1-2%) and that carried by haemoglobin (98-99%). The former is reflected in the PO2 value of blood gases. Direct measurement of percentage saturation of haemoglobin (SpO2) is possible using pulse oximetry. It is also possible to calculate SpO2 on the basis of arterial blood gases so long as shifts in the oxygen dissociation curve are taken into account. Pulse oximetry relies on the difference in permeability to light to different wavelengths between reduced and oxygenated haemoglobin. The extinction curves for each form, a function of light absorbtion, are shown in figure 2.

Figure 2: Extinction Curves, Reduced & Oxygenated Hb

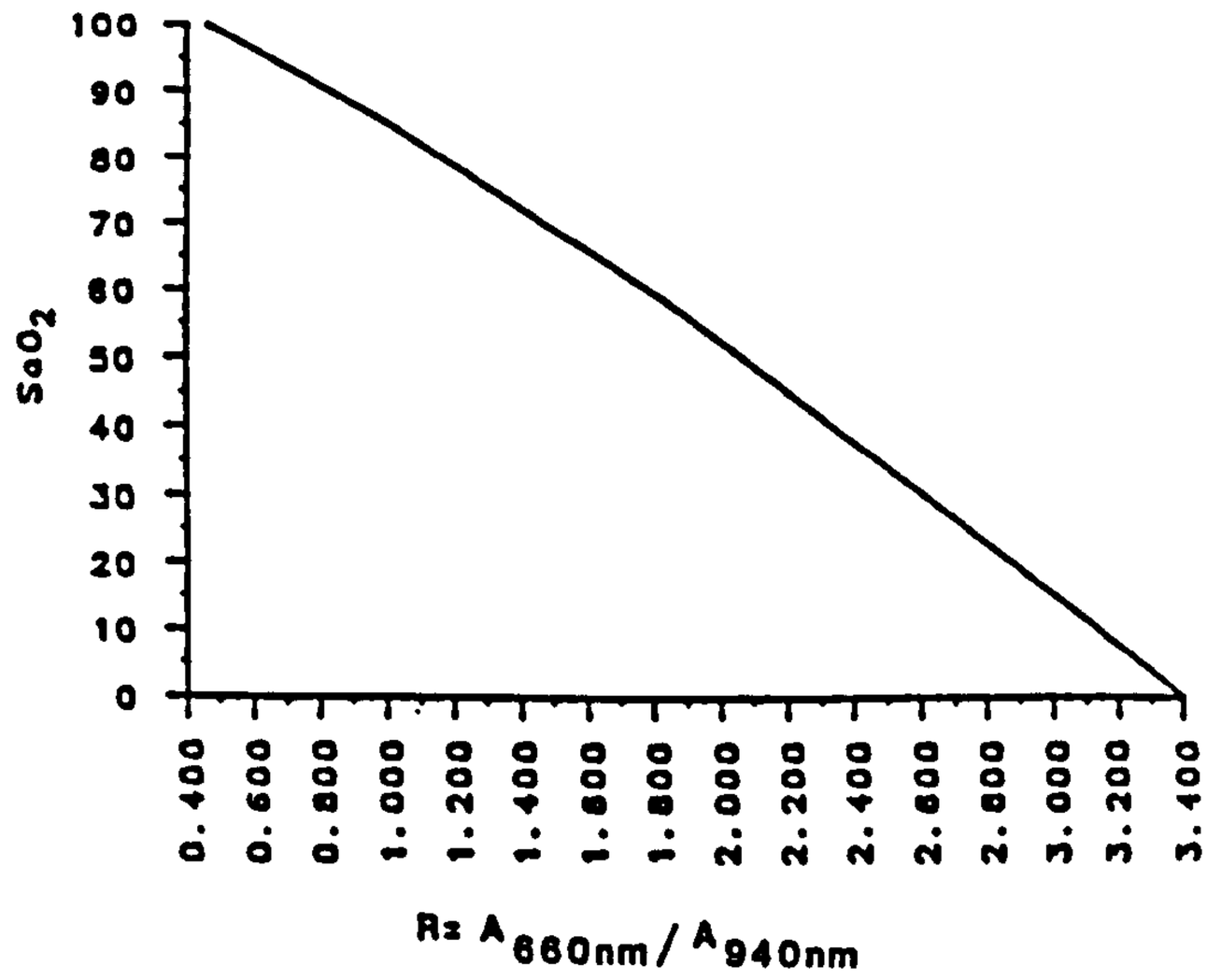


Hemoglobin extinction curves.

Reproduced from Pologue (1987)

Two light-emitting diodes one at 660 nm (red) and the other at around 920 nm (infrared) alternatively emit very bright light over a narrow portion of the electromagnetic spectrum and penetrate thick or darkly pigmented tissue and are measured on the other side. The ratio of the relative absorbency of red to infrared reflects oxygen saturation. The information obtained is used to establish a calibration curve derived empirically by correlating this ratio to invasive arterial oxygen saturation measurements (figure 3).

Figure 3: Calibration Curve/ Pulse Oximetry



. *Calibration curve used by the oximeter to calculate arterial oxygen saturation* (SaO_2) *from the ratio* (R) *of the light absorbed* (A) *by the tissue being monitored. (Figure provided courtesy of Ohmeda, 1987.)*

Reproduced from Pologue (1987)

Light transmitted through tissue consists of a constant level modulated by pulsation. It is this modulation which is of interest in % saturation measurement. The percent modulation clearly varies with vascularity and perfusion. The lower the percent modulation in relation to the constant light level the greater the gain required to achieve a usable signal and the greater the noise. Adequate perfusion and vascularisation are therefore important.

1.3.2.2 Artefact & Oximetry

Limitations of pulse oximetry have recently been reviewed (Hutton & Clutton-Brock 1993). Problems with measurement may result from motion, poor perfusion, venous pulsation (under conditions of raised venous pressure), excess ambient light, optical shunting from sensor slippage, oedema causing light scatter, severe anaemia, carbon monoxide (binding haemoglobin), methaemoglobin, fetal haemoglobin and certain nail-polish colours.

In practice, particular sources of error likely to be encountered in attempting to record oximetry during seizures are motion artefact and possibly perfusion changes.

Motion results in light absorption changes which are not filtered out if they are within physiological frequencies. Pulse oximeters analyze the waveform of the acquired signal to determine if its characteristics (shape, amplitude and timing) are as expected. It may be either rejected or used to measure saturation.

Movement artefact produces a signal of approximately the same amplitude in both red and infrared channels; thus, the ratio of the relative absorbency tends to 1. Such a ratio reads at about 85% on the calibration curve (figure 3) and readings of that order in the presence of movement need to

be interpreted with caution.

The Nellcor N200E oximeter which was used in this study has a C-lock option whereby the QRS complex may be used as the reference point for selecting the portion of the signal of interest and aligning subsequent signals to obtain a composite. This function would theoretically tend to minimise both movement artefact and the effects of poor perfusion by optimising timing of processed signals given that noise would be random with respect to cardiac activity. How much of an advantage this function adds is uncertain. It was not used in the system set up in this study. However the plethysmography signal was displayed as a separate channel to allow for the interpreter to independently accept or reject readings obtained.

Oximeters have an in-built algorithm that averages signals and weighs the contents of the existing memory more heavily than the new signal. This algorithm is guarded by manufacturers and is thus not available. The requirements of reliable measurement where there is a steady state, where an unexpected signals may be safely rejected, and a situation where a rapid response is required are clearly different. In situations where sudden desaturations may occur as in sleep apnoea for example or in ictal recordings speed of response is required. A clear lag with sudden changes in saturations has been demonstrated in all oximeters by a number of studies. This lag is greater with

finger oximetry than with ear oximetry, and is greater with desaturations than resaturation. It has also been shown to be dependent on pulse rate (West et al 1987, Severinghaus & Naifeh 1987). The Nellcor digit disposable sensor was reported to be accurate by West et al (1987) probably because the adhesive strips maintain alignment between the light transmitters and photodetectors, but substantial delays were shown at low heart rates. Kryger (1989) reports a lag of less than 10 seconds if heart rate was above 100 bpm, but a lag of 20-30 seconds with heart rates of about 50 bpm with disposable sensors (versions 55 & 57). Oximeters may also have different settings with different response times. These reflect the span of time during which the instrument averages incoming signals to obtain a mean measurement. The Nellcor 200 has 3 modes: normal response 5-7 seconds (mode 1); fast response 2-3 seconds (mode 2); slow response 10-15 seconds (mode 3). The faster the response time the more likely is movement artefact to be a problem.

Accuracy in pulse oximeters is usually better for higher saturations that lowers ones. The accuracy quotes for the Nellcor 200 by the manufacturer is as follows:

	Range	Accuracy
Adults	70-100%	+/- 2 digits
	50-69%	+/- 3 digits
	0-49%	unspecified

AIMS

2. Aims

The aims of the study were as follows:

Epidemiology

To establish the incidence and characteristics of sudden death cases in two selected cohorts with epilepsy:

i) an outpatient hospital cohort at a tertiary referral centre, and
ii) a cohort of children and young adults with epilepsy and learning difficulty.

Circumstances

To look at detailed circumstances of sudden death cases by interviewing self-referred close contacts of such cases while substantiating medical details from other sources.

Mechanisms

To investigate possible mechanisms of sudden death by recording cardiorespiratory parameters during seizures in patients undergoing videotelemetry.

Risk Factors

To define risk factors and consider methods of prevention by integrating data obtained from the different studies above.

METHODS

3. Methods

3.1 Epidemiology

Two selected cohorts with epilepsy were studied with the aim of establishing overall mortality rate and incidence of sudden unexpected death. The first was a hospital outpatient cohort and the second a cohort of children with epilepsy and learning difficulty identified at a special school (St Elizabeth's School). They will be referred to as the outpatient cohort and the St Elizabeth cohort respectively. To accurately assess mortality adequate follow-up was considered essential. The aim was therefore not only to identify deaths but also to confirm that the remaining individuals in each cohort were known to be alive. This part of the study was not aimed at identifying circumstances of death and contact with relatives was not made. Such contact was considered potentially distressing to the families and interviews were only conducted in self-referred cases (see section 3.2, pages 89 - 91).

3.1.1 Outpatient Epilepsy Cohort at a Tertiary Centre

3.1.1.1 Identification of cohort

The cohort under study included patients with active epilepsy seen in 1990 in designated specialist epilepsy clinics at the National Hospital for Neurology and Neurosurgery, the Chalfont Centre for Epilepsy (site 1), Maida Vale (site 2) and Queen Square (site 3). Patients were identified from outpatient appointment lists or from copies of clinic letters and medical notes carefully reviewed. Active epilepsy was defined to include patients who have had one or more seizures in the last 5 years or patients in remission on antiepileptic therapy. Patients with a single event or provoked seizures were included. Exclusions were noted.

3.1.1.2 Follow-Up

Date of entry to the study was that of the first outpatient clinic visit in 1990. Date of completion of follow-up was 30/6/93. Those who had attended or made contact in 1993 without missing any subsequent appointments were considered alive. General practitioners and/or the relevant Family Service Health Authority (FSHA) were otherwise contacted. A small number of patients were traced through the central register held by The Office of Population Censuses and Surveys (Southport). No direct contact with patients or

their relatives was undertaken.

3.1.1.3 Ascertainment of Causes of Death

Information regarding deaths was collected from general practitioners, hospital records, post-mortem reports, coroners reports, and death certificates as well as from information available to attending medical staff soon after death.

3.1.1.4 Patient Data

Data compiled from medical notes for the cohort included age,sex, residence (private or institutionalised), mental ability (Intelligence Quotient IQ above or below 80), years of epilepsy, epilepsy diagnosis, seizure diagnosis, estimated total number of lifetime generalised seizures, episodes of status and any associated disease, as well as EEG records in sudden death cases.

3.1.1.5 Standardised Mortality Ratios

Standardised mortality ratios (SMR) were calculated as described in section 3.4 (pages 99 - 100).

3.1.2 Epilepsy Cohort with Learning Difficulty (The St Elizabeth Cohort)

3.1.2.1 Setting - Special School

The cohort was identified at a school specialising in the education of children and adolescents with epilepsy and learning difficulty. Most pupils are boarders with epilepsy and some 50-60 pupils are resident at any one time. The school used to have an admissions policy, now reversed, whereby boys were only admitted until the age of 12.

3.1.2.2 Identification of Cohort

The cohort under study included all pupils with epilepsy who were either already attending the school on 1 April 1970 or who joined after that date and up to April 30, 1993. Pupils were identified from the school register and those without epilepsy excluded. Date of birth, date of entry to the school if after April, 1970, and date of leaving school were recorded. Intelligence quotients were obtained from school records in approximately half the cases. Epilepsy was severe in the majority. Most pupils had more than one seizure per week with some having several seizures daily. Those seizure-free for greater than one month were the exception.

3.1.2.3 Measures Regarding Seizures

The school has a high staff student ratio. Four attending members of staff are present each night in addition to an on-site on call nurse. In 1974/75 a continuous nocturnal sound monitoring system was installed. When a pupil is seen or heard to be in a seizure someone remains in attendance until he or she is judged to be stable adjusting position and ensuring adequate respiration. The on-call nurse may administer rectal diazepam or paraldehyde as required. Back-up cover is provided by the local general practitioners with transfer to hospital if necessary. Specialist advice is arranged on an individual basis, although a neurologist with an interest in epilepsy visits the school on a regular basis. 'Smother proof' pillows are used at the school (The helping hand, 2 Chester Road, Macclesfield, SK 10 1AU). Administration of medication is closely supervised.

3.1.2.4 Follow-Up

Pupils were considered alive if still at the school at the end of the study, or, in the case of ex-pupils, if they were known to be alive by the school staff during the preceding year. The remaining pupils were traced via the Office of Population Censuses and Surveys (OPCS), where the national registers for births, marriages and deaths are held. Deaths were either known to the school staff or were

identified by OPCS. Follow-up duration extended from date of entry to the study (April 1, 1970 or school entry date if later) until 30 April 1993 or date of death. Thus, follow-up included a period of residence at the school as well as time after leaving. To calculate years of follow-up under the direct supervision of the school, it was assumed that children spent 245 days a year at the school and 120 days a year on leave.

3.1.2.5 Circumstances & Causes of Death

Circumstances relating to known deaths were compiled from information available to school staff, death certificates, coroner's officers reports, and post-mortem examination results. No contact was made with relatives for the purpose of this study. Cases were classified as sudden unexpected deaths in epilepsy (SUDEP) if no cause of death was found and included cases with evidence for a seizure.

3.1.2.6 Standardised Mortality Ratios

Standardised mortality ratios (SMR) were calculated as described in section 3.4 (pages 99 - 100).

3.2 Interviews With Bereaved Contacts

The aim of the above two studies was primarily to establish as accurately as possible incidence of sudden unexpected death in the cohorts under study. Although it was also possible to compile some details of circumstances, these were inevitably incomplete, particularly that contact with relatives was not made as part of the study.

In an attempt to look at detailed circumstances of death in SUDEP cases, a separate study was undertaken where interviews with close relatives of such cases were undertaken. In view of the sensitive nature of the subject, relatives were not approached directly but were self-referred mainly through the self-help group "Epilepsy Bereaved?" with a few via medical colleagues. Semi-structured interviews based on a questionnaire (see appendix 7.3) lasting 1-2 hours were mostly held at the National Hospital for Neurology and Neurosurgery and were usually jointly conducted by the same two interviewers, myself and a nursing colleague (S.G.) with an interest in epilepsy. Only 3/27 interviews were conducted by S.G. alone. Circumstances of death were covered in full as well as a detailed medical and social history. Relatives were encouraged to attend accompanied with phone interviews carried out where necessary. Information from other sources included death certificates, summary of the coroner's

officer's report and post-mortem examination results. Previous physicians were usually contacted for further confirmation of medical details. Classification in terms of seizure types and diagnosis of epilepsy syndrome was based on the recommendations of the Commission on Classification and Terminology of the International League against Epilepsy (1989 - appendix 7.5).

Given the painful nature of memories evoked during the interviews, every effort was made to minimise any distress. Relatives were given ample time to express views and address issues of concern, while at the same time specific comments on the part of the interviewers regarding clinical management were avoided. On the whole relatives welcomed the opportunity to share their loss and help in medical research.

3.2.1 Classification

Cases were divided into four categories:

- Exclusions if there was diagnostic doubt regarding the history of epilepsy or terminal event

- Cases with sudden death in patients with epilepsy where an abnormality was found at post-mortem that was likely to have contributed to the person's demise

- Cases with sudden unexpected death in patients with chronic epilepsy with or without evidence for a seizure where post-mortem examination did not reveal a cause for death

- Unclassified cases

3.2.2 Analysis

Information was analyzed with particular reference to whether the death was witnessed, whether there was evidence in favour of a seizure, the position in which the body was found, control of epilepsy, medication history and the presence of other potentially relevant factors.

This study will be referred to as the interview study.

3.3 Ictal Cardiorespiratory Parameters

In this study, patients with epilepsy undergoing routine EEG/Video telemetry were recruited for additional recording of cardiorespiratory parameters.

3.3.1 Setting

The tests were performed in the EEG/Video telemetry unit at the National Hospital for Neurology and Neurosurgery. During the period of study usually only one (at most two) of the systems available for prolonged recording were adapted for the extra recordings required.

3.3.2 Patients

Patients with a probable diagnosis of epilepsy admitted for EEG/Video telemetry and booked to have their recording on the adapted system were recruited. Patients booked for one overnight recording only were not approached to avoid any initial interference/artefact problems affecting their routine recording. Patients approached did not represent all patients undergoing telemetry at that unit during the period of study as some had recordings performed using systems not set up for the additional recordings. Following consent they were left to get accustomed to the routine EEG/ECG electrodes overnight before the additional

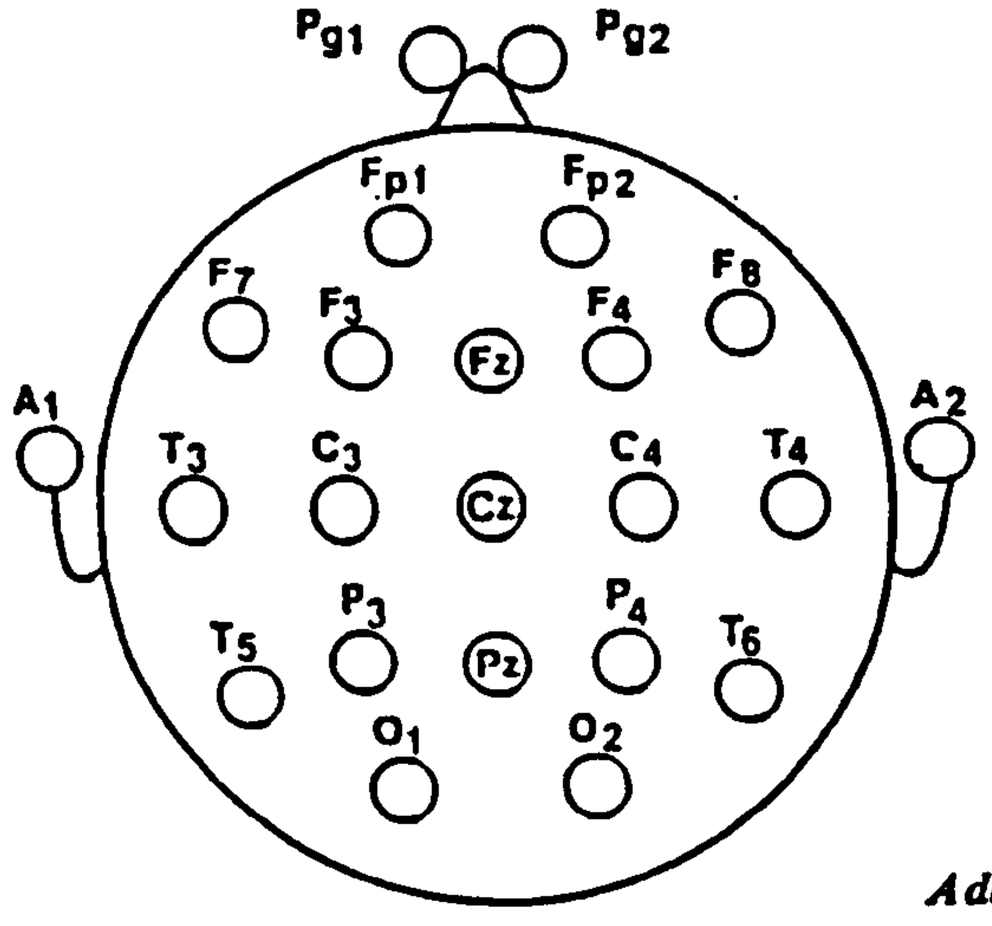
electrodes were applied. All patients monitored with the appropriate equipment with a likely diagnosis of epilepsy were approached unless their physician wished otherwise (one case). An information leaflet as approved by the local ethical committee was supplied to each patient (appendix 7.2). Patients reported on in this dissertation were recruited between February 1994 and November 1994.

3.3.3 Equipment & Electrodes

3.3.3.1 Routine Telemetry Recordings

The system used for routine recordings, which was adapted for the additional parameters, was developed in house and had been designed and assembled by the department physicists; it can record up to 32 channels of digitally acquired data with a sampling rate of 200 Hz. EEG electrodes (silver/silver chloride) are normally applied using collodion following the international 10-20 system (Figure 4). Additional electrode placements include superficial sphenoidal electrodes applied routinely with occasional other electrode placements if required. ECG is routinely recorded. EMG and EOG electrodes are also usually used. Video/Audio monitoring is routine with timing synchronised with EEG data.

Figure 4: 10-20 System



Adapted from EEG Primer,
R. Spehlmann, Elsevier Biomedical

Adapted from Spehlmann (1987)

3.3.3.2 Additional Parameters

In addition to Video/Audio and 27 channels of EEG/ECG/EMG/EOG the following were recorded as per guidelines for polysomnography (American Thoracic Society Consensus Conference) and as outlined in section 1.3 (pages 75 - 81).

- Pulse oximetry using a Nellcor oximeter (N200E) and single patient use disposable digital probes (Nellcor Adult Oxisensor D-25). The setting chosen was the normal setting

(see section 1.3.2.2, page 81). The disposable probes were usually placed on the ring finger of the non-dominant hand and were chosen as they were easily applied and maintained in position over long periods of recording.

Different movements were tried in a controlled setting to determine the effect of movement artefact on SpO2 readings with the equipment used in this study. In practice, although SpO2 readings could be made to drop with movement to levels as low as 60%, movement was much more likely to result in SpO2 readings of 80% or above. Changes in SpO2 recorded depended on the type of movement. Violent or excessive movement of the whole limb sometimes resulted in the readings cutting out to 0% and therefore did not pose a problem with interpretation. Tonic posturing of the upper limb did not generally result in significant drops of SpO2. The most likely movements to result in drops below 80% involved flexion at the distal interphalangeal joint at a frequency comparable to pulse rates. Such movements do not generally occur during seizures. Plethysmography signal was recorded and displayed to allow for the interpreter to independently accept or reject oximeter readings obtained.

- Airflow was recorded using a disposable mouth and nose airflow thermistor (Nellcor Adult Airflow Sensor, Model 971).

- Respiratory effort was recorded by inductive plethysmography (Kryger 1989) using chest and abdominal bands (Respitrace). These were secured in place using Coban (3M). Changes in the cross-sectional area of the abdominal and rib cage compartments result in changes in the inductance of the transducers which can then be measured.

3.3.3.3 Data Storage & Display

Data was recorded onto a) Video tapes and b) rewritable optical discs (Panasonic). After review the latter was permanently stored on digital audio tape. Seizures recorded on video were all retained.

All data, excluding the video recording, was simultaneously displayed on a play-back system that allowed for remontaging, adjustment of gain per channel, high frequency filter and channel selection. All 32 channels could be viewed together at any one time. Epochs could be reviewed at 10 or 20 seconds per page and plotted at 10 to 40 seconds per page. Oximetry data, which was displayed at the same time as other data, was also extracted separately and plotted for variable periods extending over many hours per page.

3.3.3.4 Analysis

Video Recording

All clinical seizures were reviewed on video with particular reference to the following:

1. Seizure characteristics to help in classification of seizure type and lateralisation, including the presence or absence of dystonic or paretic posturing of limbs, automatisms, vocalisation, alterations in speech, head/eye deviation and tonic/clonic movements.

2. Assessment of respiratory rate/rhythm. In this regard vocalisations/ sound recordings were often useful as was fast-playback of the seizure.

EEG

In addition to assessment of the interictal recording, EEG changes during seizures were examined and categorised as follows:

a) no definite EEG change (including slight attenuation of background activity or movement artefact).
b) nonspecific EEG change including slow activity.
c) clear rhythmic discharge with lateralisation or localisation also used categorize the seizure along with other information.
d) clear attenuation of background rhythm

ECG

Baseline ECG rate (expressed as beats per minute) was determined for 10-20 second epochs. Maximum and minimum rates were determined if the latter differed by more than 10 bpm from baseline. In addition the longest RR interval was measured.

Oximeter & Plethysmography

Extracted plots of oximeter readings could be obtained and plotted over many hours. In addition, during each seizure the readings were reviewed in plots of 10-40 epochs per page to ensure that changes were gradual, consistent and appropriate, with relative preservation of the plethysmography signal (see section 1.3.2.2, pages 79 - 81).

Respiratory Pattern

Baseline respiration just prior to and following the seizure was assessed in terms of excursions produced by the airflow sensor, abdominal and rib bands, to ensure adequate recording. Changes noted during seizures included the presence or absence of apnoea, central or obstructive, and its duration. Other alterations in respiratory pattern were noted as well the relationship between apnoea, hypoxia and bradycardia. Apnoea was defined as respiratory arrest lasting more than 10 seconds. Obstructive apnoea was considered to be present if good respiratory effort was accompanied by reduced or absent airflow.

Although each parameter is separately described here, it must be stressed that interpretation was only possible on the basis of integrated information from all sources.

Clinical Data

Clinical information relating to each patient was obtained after review of medical data and included age, sex, years of epilepsy, epilepsy syndrome, interictal EEG, aetiology of epilepsy, MRI/ other radiological data where available, and pathological data if surgery was later performed.

3.4 Data Processing & Statistical Analysis

Epi Info[3] was used to enter data. Chi-squared test was used for comparing discrete variables. Fisher's exact test was used in comparing discrete variables where the expected frequencies were small.

Epidemiology:

Standardised mortality ratio (SMR) is the ratio of number of deaths observed in the group under study to that expected to have occurred during the follow-up period if the group had experienced the same age and sex-specific death rates as the general population (Morris & Gardner

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[3]Epi Info, Version 5: A Word Processing, Database and Statistics System. Centre for Disease Control, Atlanta, Georgia and The World Health Organisation, Geneva Switzerland. Distributed by USD, Incorporated 2075A West Park Place, Stone Mountain, GA 30087

1988). In both the outpatient cohort and the St Elizabeth cohort, person-years in 5-year age bands for each sex (Kahn & Sempos 1989) were calculated using date of birth, date of entry to and date of exit from the study. Expected mortality was calculated based on mortality rates for England and Wales. Published rates for 1991 (OPCS Series DH1 no 18) were used for the outpatient cohort. The period of follow-up during this study extended from 1990 to 1993, but published rates for 1991 did not differ from those of recent years and were thus considered representative. In the St Elizabeth cohort, the period under study extended from 1970 to 1993 and expected mortality was calculated based on average mortality rates published for the years 1971-1990 for England and Wales (OPCS Series DH1 no 25). 95% confidence intervals for SMR were calculated with upper and lower values derived from Poisson Distribution Tables (Gardner & Altman 1989).

RESULTS

4. Results

4.1 Epidemiology

4.1.1 Outpatient Cohort

4.1.1.1 Characteristics of the Cohort

The cohort comprised 601 patients (330 males, 271 females) with an age range at entry of 10-80 and mean age of 32.5 years (Figure 5). Total follow-up amounted to 1849 patient-years (average 3.076 years per patient). Duration of epilepsy ranged from less than a year to 63 years with a mean of 19 years (1.3% unknown). Table 6 lists the breakdown in terms of epilepsy diagnosis based on the modified 1989 International League Against Epilepsy Classification (Commission on Classification and Terminology 1989 - appendix 7.5). 40.6% were seen at site 1, 8.5% at site 2, 47.6% at site 3 and 3.3% at more than one. Patients at site 1 differed from the rest in that they were more likely to have IQ's of less than 80 (44% of those at site 1, vs 7.8% at site 2 and 15% at site 3 with 1.8% of cohort unknown, $P<0.0001$) and were more likely to reside in some form of supervised accommodation (25.8% of those seen only at site 1, vs 3.9% at site 2 and 5.2% at site 3 with 3.0% of cohort unknown, $P<0.0001$). Of 590 cases where the information was obtained, 11.9% had a history of one or more episodes of generalised status and 2.7% had a history

of non-convulsive status recorded. In 473 records, total lifetime generalised tonic/tonic-clonic seizure count was estimated; 11.8% had none, 18.8% had less than ten, 21.8% had between 10 and 100, 37% had greater than 100, and 10.6% greater than ten (number uncertain).

Figure 5: Outpatient Cohort, Age in 5-Year Bands

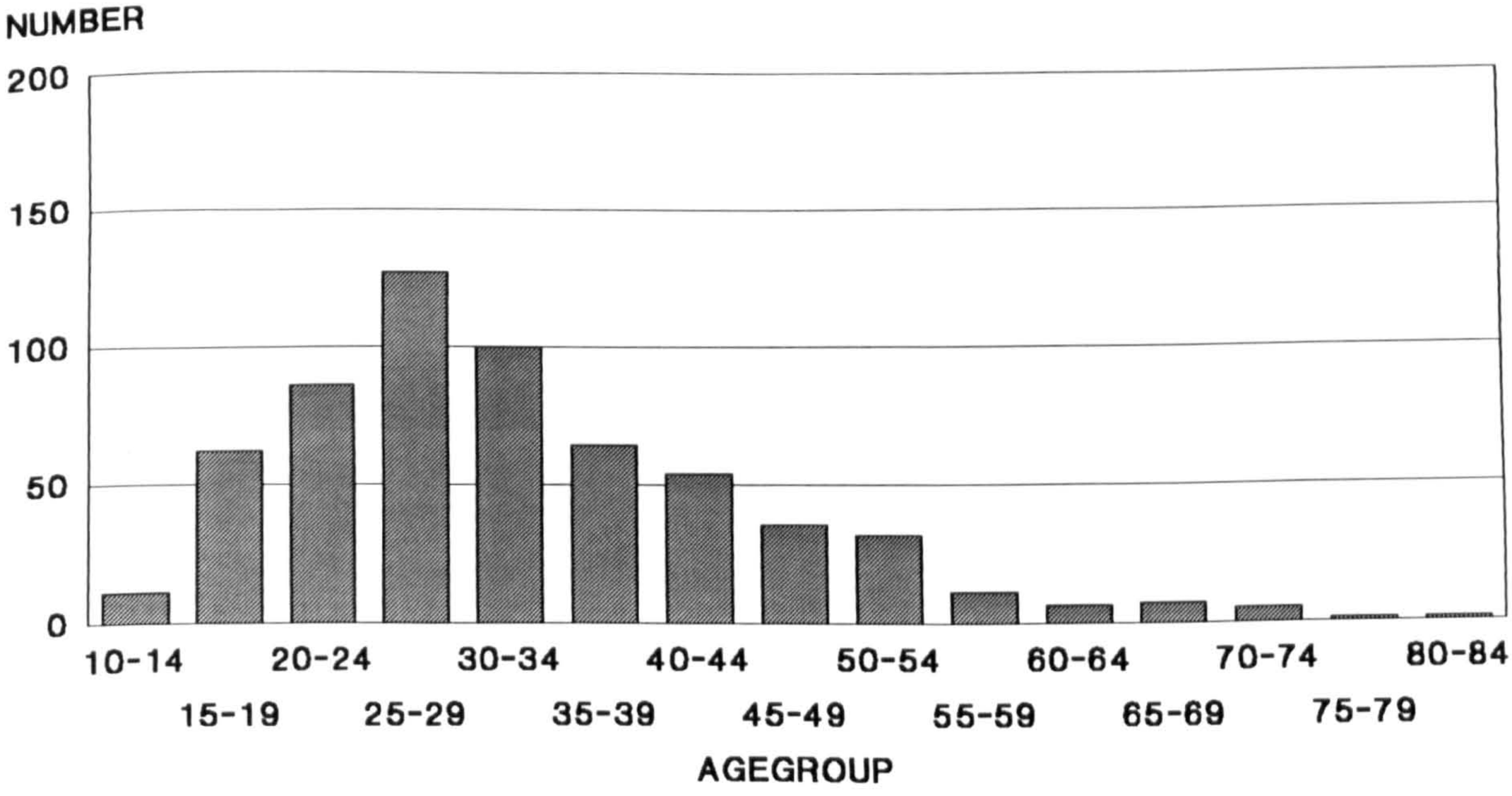


Table 6: Epilepsy Diagnosis in Outpatient Cohort

Localisation related	
symptomatic or cryptogenic	401 (66.7%)
Generalised epilepsy	
idiopathic	76 (12.6%)
Generalised epilepsy	
cryptogenic or symptomatic	47(7.8%)
(9 specific syndromes)	
Undetermined	65 (10.8%)
Situation related	
(3 provoked, 1 isolated)	4 (0.7%)
Unknown	8 (1.3%)

4.1.1.2 Exclusions

Details of exclusions are shown in table 7 with the largest category that of patients with unrelated neurological disease.

Table 7: Outpatient Cohort, Exclusions

Unrelated Neurological Disease	70 (53 %)
Non-epileptic attacks[1]	17 (12.9%)
Recurrent attacks - cause unknown	15 (11.4%)
Syncope	5 (3.8%)
Undiagnosed single blackout	1 (0.8%)
Administrative[2]	24 (18.3%)
TOTAL	132

1 Including pseudoseizures, hyperventilation and panic attacks

2 Listed names not satisfying inclusion criteria

- Listed new patients - did not attend	- 5 (3.8%)
- Patients with Epilepsy	
. not seen in 1990	-12 (9.1%)
. not seen in designated clinics	- 3 (2.3%)
- Patients without epilepsy	
. not seen in 1990	- 3 (2.3%)
. not seen in designated clinics	- 1 (0.8%)

4.1.1.3 Overall Mortality

Only one patient from the cohort of 601 remains untraced; 3 other patients, known to be medically stable, moved abroad during the period under study. All 4 were considered alive for the purpose of analysis.

A total of 24 patients died (mean age at death 35, range 18-73) during the follow-up period representing an overall mortality of 1:77 per year and a standardised mortality ratio (SMR) of 5.1 (95% confidence intervals (CI) 3.3-7.6), 4.4 for men (CI 2.4-7.5) and 6.3 for women (CI 3.2-11.3). Causes of death are listed in table 8. In 5/24 cases (21%) the clinic medical staff were unaware that the patient had died. SMR for deaths from neoplasms excluding brain tumours (3 patients) was 2.16 (CI 0.45 - 6.32). Mean duration of epilepsy in these patients was 17 years (3-37).

Table 8: Outpatient Cohort, Classification of 24 Deaths

Neoplasms[1]	5
Accidental[2]	3
Spontaneous Intracerebral Haemorrhage[3]	2
Sudden unexpected deaths[4]	11
Status (complications thereof)	1
Other[5]	2

1. 2 gliomas, 1 each acute myeloid leukaemia, pelvic chondrosarcoma and lung adenocarcinoma)
2. 2 Head injuries (1 witnessed seizure-related), 1 drowning in bath
3. 1 vascular malformation, 1 bleed into probable tumour
4. including two with possible additional factors - see text
5. 1 severe pancreatitis - no evidence of gallstones/alcohol
   1 herpes simplex encephalitis

4.1.1.4 Sudden Unexpected Deaths - Including Seizure-Related

There were 11 (6 female, 5 male) unexpected sudden deaths among the cohort. One was known to be of Asian extraction, the remainder being Caucasian. Only one was not referred to the coroner and was certified in the community as having died of an epileptic seizure. In two female cases, both reported as being well on the day of death, additional factors were present. One had an incidental one-week old subdural haematoma at post-mortem that was not thought to be the cause of death. Another patient, with known chronic renal failure and evidence in favour of a convulsion immediately preceding death, was found to have a very high level of a recently introduced antihypertensive drug, other drug levels being within the accepted range. The findings on coroner's post-mortem performed in 10 out of 11 cases revealed moderate to severe pulmonary congestion in 8, mild congestion in one and clear lungs in the remaining case. One patient had severe congestion of all organs including the brain.

Mean age at death was 28.6 years (range 18-34) and mean duration of epilepsy 20.8 years (range 14-30). Sudden deaths observed in relation to patient years are shown in table 9. An overall incidence of the order of 1:200/year was observed and 1:100/year taking the age-group 15-34. One patient had severe mental handicap, and 4 other patients

had IQ's below 80. There was no difference in the incidence of sudden death between patients seen at the three sites. The classification of the seizure-disorder was: 5 localisation related (symptomatic or cryptogenic), 1 idiopathic generalised, 3 cryptogenic or symptomatic generalised, 2 undetermined (both focal and generalised features). 3 patients had a known past history of generalised status and all had a history of generalised tonic clonic seizures. All but one were considered medically intractable by their physicians. 3 were living in supervised accommodation. Mean number of antiepileptic drugs as recorded on the last hospital clinic attendance was 2.36 (range 1-4) and included acetazolamide (1), carbamazepine (7), clobazam (2), clonazepam (1), lamotrigine (1) phenobarbitone (1), phenytoin (5), primidone (2), sodium valproate (4) and vigabatrin (2).

Table 9: Outpatient Cohort: SUDEP, Person Yrs & Age

Age (years)	person years	sudden deaths
14 or under	13	-
15-34	1109	11*
35-54	604	-
55-75	106	-
> 75	17	-

* Including two with possible additional factors - see text

Some evidence in favour of a seizure was found in 6/11 cases (bitten lip(1), bitten tongue(2), found partly or fully off bed(3) with noise heard consistent with seizure(1) and in an additional case the death certificate stated seizure. 6/10 patients where the information was available died a variable period after retiring to bed. Eight of these deaths were unwitnessed. Of the remaining three cases, information was not available in one, the onset of the collapse was unwitnessed in another and in the third available details were incomplete.

EEG records belonging to 10/11 sudden death patients were reviewed. 8/10 had epileptiform activity in at least one interictal record with 5/10 showing generalised discharges. These 8 patients showed persistence of epileptiform activity across serial recordings (32/34 recordings, range per patient 2-10). ECG recordings were only available as part of the EEG record in 3 cases and QT corrected for heart rate was within the normal range[4].

Causes of death as recorded on the death certificate are

---

[4]QT = beginning of QRS complex to end of T-wave
corrected QT (QTc) = measured QT interval divided by the square root of the RR interval

Normal values: QTc = 0.33 - 0.47 (Greenfield 1988)

Patients:

Heart rate	QT-interval	QTc
56	0.38	0.37
59	0.37	0.37
69	0.40	0.43

listed in table 10. One of the SUDEP cases was also part of the St Elizabeth cohort.

Table 10: Outpatient Cohort, SUDEP, Death Certificates

- Ia Epilepsy	1
- Ia Acute Epileptiform Convulsion	1
- Ia Acute Epilepsy	1
- Ia Epileptic Fit	1
- Ia Chronic Epilepsy	1
- Ia Idiopathic Epilepsy	1
- Ia Status Epilepticus	2
- Ia Pulmonary Oedema & Congestion Ib Status Epilepticus II Brittle Epileptic	1
- Ia Status Epilepticus II Subdural Haematoma of Rt Temporal Region	1*
- Grand mal epileptic fit due to lowering of blood pressure due to an overdose of anti-hypertensive drug	1*

* see text

4.1.2 The St Elizabeth Cohort

4.1.2.1 Characteristics of the Cohort

During the period under study 310 pupils with epilepsy (103 males, 207 females) and 8 pupils without epilepsy were registered at the school. The latter will not be considered further. Mean age at entry to the school was 11 years (range 4.9-18.4) and mean age at leaving school was 15 (range 6-24). Intelligence quotients from 177 (57%) school records reviewed are shown in table 10.

Table 11: St Elizabeth Cohort, IQ - Intelligence Quotients 177/310 (57%) School Records (range: unrecordable - 100)

Not quoted in notes	21 (12%)
Average (90-109)	12 (7%)
Low average (80-89)	20 (11%)
Borderline (70-79)	21 (12%)
Mild Mental Handicap (55-69)	41 (23%)
Moderate Mental Handicap (40-54)	37 (21%)
Severe and Profound (-39)	25 (14%)

Total duration of follow-up was 4135 years (females 2984, males 1151; f:m ratio 2.6:1) with an average of 13.34 years/pupil. These included 1289.6 years at the school

(865.9 excluding holidays) and 2845.7 years after leaving (3269.3 years if holidays while enrolled at the school are added to time after leaving). The OPCS were involved in tracing 123 pupils of whom 5 have not been fully traced. They are considered alive for the purpose of analysis as the OPCS does not list them as having died.

4.1.2.2 Overall Mortality

There were 28 deaths (20 females, 8 males, female:male ratio 2.5:1) identified (9 by OPCS) during the follow-up period with a mean age at death of 19 years (range 9-32). Death certificates were available in all but one. Standardised mortality ratios are shown in table 11 and classification of deaths in table 12.

Table 12: St Elizabeth Cohort, SMR

Age	Person Yrs		Deaths		Mortality ratios/95% CI Intervals		
	F	M	F	M	F	M	F+M
1-4	-	0.2	-	-	-	-	-
5-9	122.4	150.6	-	1	-	22.7(0.6-127)	-
10-14	539.7	348.5	3	5	29.1(6-85)	49.7(16.1-116)	39.3 (17.0-77.5)
15-19	859.5	320.8	6	1	21 (7.8-46)	3.9(0.1-21.8)	13(5.2-26.8)
20-24	713.9	206.0	4	1	15.3(4.2-39.2)	5.4(0.1-30.0)	11.2(3.6-26.1)
25-29	464.1	100.8	5	-	25.0(8.1-58.3)	-	-
30-34	238.8	24.6	-	-	13.6(1.65-49.3)	-	-
35-39	45.5	-	-	-	-	-	-
40-45	0.2	-	-	-	-	-	-
total(F)		2983.9	20		18.8(11.5-29.0)	-	-
total(M)		1151.4		8	-	11.5(5-22.7)	-
Total (M+F)	4135.3		28		-	-	15.9(10.6-23.0)

Table 13: St Elizabeth Cohort, 28 Deaths

Neoplasm	3[1]
Accidental	3[2]
Sudden Unexpected Deaths	14[3]
Status Epilepticus	4[4]
Other	3[5]
Uncertain	1[6]
Total	28

1. Glioma 1 ; hydrocephalus/oligodendroglioma 1; astrocytoma/tuberous sclerosis 1

2. Road traffic accident victim following seizure 1 ; Drowned 2: seizure excluded in one; said to have drowned in the bath in the second - death certificate not available

3. Full documentation is not available in two cases - see text

4. 3 cases with status epilepticus listed on death certificate and substantiated through other sources including 1 with Rasmussen's Encephalitis; in the fourth case only the death certificate was available; some doubt therefore remains

5. Acute asthmatic attack 1
   Respiratory failure secondary to congenital, kyphoscoliosis/cerebral palsy 1
   General debility/ chronic pressure ulcers/epilepsy 1

6. Difficult to classify on the basis of the death certificate, the only source available:
   1a Cerebral Anoxia, 1b Grand mal epilepsy 1c Hydrocephalus

4.1.2.3 SUDEP Cases

Fourteen cases were classified as probable SUDEP cases with 1 further case unclassified (table 12). One of the SUDEP cases was also part of the outpatient cohort. Death certificates were available in 14/14, and post-mortem reports in 11/14. Twelve of the fourteen SUDEP cases had been referred to the coroner and coroner's reports were available in 11. Of the two deaths not referred, detailed circumstances were available in one as the death occurred while the ex-pupil was resident in a long-stay institution. The other was certified in an acute hospital but notes could not be traced. The death certificate stated that the mother was present at the death.

Table 14 summarises circumstances in the SUDEP cases. In 10/12 of these cases where the information was available the deaths were unwitnessed. In one, a partner, also with learning difficulty, assumed the person was asleep following a seizure. In another the person was found collapsed but of normal colour. Help was called by which time she had become cyanosed and resuscitation was unsuccessful.

Pulmonary oedema was recorded at post-mortem in 11/11 available reports, and brain oedema in 6/11. Tongue biting was present in 3/11. Toxicology at post-mortem was performed in at least 7 cases, including one where there

was circumstantial evidence of excessive phenobarbitone ingestion. Post-mortem phenobarbitone level however was 3.8 mg%, with phenobarbitone found in the stomach. In three cases the position in which the body was found as well as the presence of secretions, petechial haemorrhages and pressure markings suggested asphyxiation.

Table 14: St Elizabeth Cohort, Circumstances in SUDEP Cases

Age	Sex	Circumstances	Death certificate
10	F	found dead in bed a.m.[1]	Epilepsy
17	F	found dead pm/bedroom floor[1]	Status Epilepticus
18	F	found dead in bed[1]	Acute Epilepsy
18	F	found dead p.m. on floor[1]	Status Epilepticus
20	F	unconfirmed[2]	Accidental suffocation/ due to idiopathic epilep.
20	F	found dead a.m. on floor[1]	Acute Epilepsy
23	F	unconfirmed[3]	Brain death/ Prolonged epileptic fit
25	F	found dead in bed a.m.[1]	Acute respiratory failure due to epileptic attack
28	F	found dead in bed a.m.[1]	Asphyxia/ Epileptic fit
28	F	died after seizure[1,4]	Idiopathic Epilepsy
12	M	found dead a.m.on floor[1]	Postural Asphyxia/ Epilepsy
14	M	found on toilet floor a.m.[5]	Grand mal Epilepsy/ Severe Subnormality
16	M	found dead in bed a.m. vomited/no aspiration on pm[1]	Hypoxia/ Status Epilepticus
22	M	found collapsed at home[1]	Status Epilepticus

1. As stated in coroner's officer's report compiled at the time of death.
2. Case referred to coroner but archives destroyed in 1975
3. Death certificate issued in hospital, but notes not found
4. Seizure seen by husband (learning difficulty) who assumed she was asleep
5. As documented by the hospital where the patient was a long-term resident

Mean age at death for the SUDEP group was 19 years (range 10-28) with a mean duration of epilepsy of 17 years (range 8-26). Previous mean Full Scale Intelligence Quotient in 13/14 cases, was 65 (range 40-98); a further case was described as globally retarded. In all these cases there was a history of generalised convulsive seizures. None of the SUDEP cases occurred while the pupils were under the supervision of the school (865.9 person years) and 14/14 deaths occurred either after the pupils had left the school (12) or while on leave (2) (3269.3 person years) (X^2 test, P = 0.075). In two separate cases, fatal episodes of collapse occurred on the school premises: one was due to an acute asthmatic attack, and the other an episode of serial seizures/ status epilepticus with the child dying a few weeks later in hospital. Table 15 shows the observed sudden SUDEP cases in relation to person years.

Table 15: St Elizabeth Cohort, SUDEP, Age & Person-Yrs

Age-group	SUDEP No	Person Years	1:Person Years
1-4	-	0.2	-
5-9	-	273	-
10-14	3	888	1:296
15-19	4	1180	1:295
20-24	4	920	1:230
25-29	3	565	1:188
30-34	-	263	-
35-39	-	45.5	-
40-44	-	0.2	-

4.2 Interview Study

27 interviews (3 by phone) were carried out between February 1993 and September 1994. Key persons interviewed included parents (19), siblings (3), spouses/partners (4) and a key-worker (1) and information was supplemented by relevant eye-witness accounts in two cases. Details are in tables 16 and 17.

Table 16: Details of Interviews

Interval between interview and death		
All Cases	(SUDEP cases)	
10	(7)	within one year of death
7	(6)	1-2 years
7	(6)	2-5 years
1		7 years
1		20 years
1	(1)	29 years
Body found or death witnessed by one of interviewees		
17/27 All cases, 11/20 SUDEP cases		
Contact between deceased and interviewee		
All Cases	(SUDEP cases)	
18	(12)	daily
7	(6)	weekly
2	(2)	monthly

Table 17: Interviews, Other Sources of Information

Category	Certified Cause of Death	Post-mortem Report	Referred to coroner + coroner's post-mortem	Coroner's Summary of History	Previous Records/ Clinical Summary	EEG Reports
Exclusions (3)	3/3	3/3	3/3	2/3	2/3	1/3
SUDEP cases (20)	19 + 1*/20 *= details from tape of inquest	18 + 1* /20' *= details from tape of inquest '=one missing archives not kept	20/20	16+1*/20 *=details from tape of inquest	17*/20 *= + one with notes of terminal event only	19/20
Mechanism suggested by post-mortem (4)	4/4	4/4	4/4	2/4	2/4	2/4

4.2.1 Exclusions

Three of 27 cases were excluded.

In one case there was doubt about the diagnosis of epilepsy in a previously untreated teenager whose presentation was a terminal collapse involving rigidity but no clonic movements.

The collapse was immediately preceded by a feeling of dizziness while sitting which he described to a friend as like getting up too fast. He had had headaches requiring analgesia for two months but had otherwise been well. Early history consisted of two breath holding attacks in infancy and two other events at the age of 2. The first consisted of a convulsion associated with a fall, the onset of which was not witnessed, and it was not clear which had occurred first, and the second a brief episode of altered behaviour. His sister had a history of 2 non-febrile convulsions. No other first degree relatives had epilepsy but there was a family history of epilepsy in distant relatives. He was resuscitated by on-lookers but later died in intensive care and was an organ donor including of the heart. Post-mortem in addition to anoxic damage and brain oedema showed what was described as more chronic inflammatory changes in the medulla suggestive of a viral encephalitis. CSF had been reported as normal. "Epileptic fit" was certified as the cause of death (Ic).

Two other cases were excluded because dry drowning (Greene 1965) could not be ruled out. In one case the face was entirely submerged in bath water and in the other it was partially so. Another, found dead in the bath with a bitten tongue, and no evidence of immersion, was included.

4.2.2 Sudden Unexpected Deaths with Mechanism Found at P.M.

Four of 27 cases were sudden and unexpected non-traumatic death

in individuals with chronic epilepsy where post-mortem findings indicated a cause of death.

Two (aged 34 & 63) were witnessed to have their habitual generalised tonic clonic seizure (TCS) lasting 2-3 minutes and died immediately after. They had significant ischaemic heart disease at post-mortem considered to be the cause of death in both cases. Epilepsy was recorded as a contributory factor (under II) in the death certificate in only one of the two cases, despite the clear observation of a habitual seizure at the time of death.

One (aged 10, idiopathic primary generalised epilepsy) was heard to convulse and was found collapsed shortly after having vomited. Post-mortem showed aspiration. The larynx, trachea and major bronchi as far as third generation bronchi contained partially digested food, with the lungs showing extensive patchy atelectasis and congestion most marked within the right lower lobe but present within all lobes of both lungs. The fourth case, aged 24 with idiopathic primary generalised epilepsy, was found with a bitten tongue and a food bolus occluding the larynx on post-mortem.

4.2.3 Sudden Unexpected Deaths

Twenty of 27 cases (10 F, 10 M) fulfilled the definition of SUDEP (page 17). Age-range at death was 14-51 years (mean 27) with 19 aged between 14 - 36. Mean age of onset of epilepsy was

14 (range 1-30) with a mean duration of 12 years (range 1-29). Eight were in full employment, 2 part-time, 5 were students, 1 was a pupil and 4 were unemployed. At least 16 were of normal intelligence. A history of self-harm was obtained in one case. All but one (both Asian and Caucasian ancestry) were Caucasian.

4.2.3.1 Syndromic Diagnosis in SUDEP Cases

Table 18 lists the syndromic epilepsy diagnosis as well as EEG findings in 20 SUDEP cases. This classification was based on a full history taken from those interviewed, medical notes where obtained and EEG findings. Patients were classified as having primary generalised epilepsy if a previous EEG had shown a generalised spike wave disturbance and the clinical syndrome was consistent. Only previous EEG reports were available rather than the actual records. Additional reported variable 'focal' EEG findings were not considered a reason to reclassify the patient if there was no clinical indication of a partial seizure disorder. One patient, however, with an aura suggestive of a focal onset and generalised spike/wave on EEG was classified as undetermined. A further patient with TCS, absences, myoclonus, photosensitivity on EEG and no evidence of progressive neurological disease was classified as primary generalised despite a borderline IQ of 75. CT and MRI scanning had been performed in at least 9 and 2 cases respectively. ECG/ECG reports were only available in 2 cases but no family history suggestive of an inherited predisposition to sudden non-ischaemic cardiac death was obtained.

Table 18: Interviews, Epilepsy Diagnosis in 20 SUDEP Cases

DIAGNOSIS		EEG generalised spike/wave paroxysmal discharge	EEG Photosensitivity demonstrated	EEG focal abnormalities
GENERALISED EPILEPSY (10)				
Primary generalised epilepsy (8)		7 + 1*/8 * generalised slow wave bursts & occasional spikes	3/8	3/8
	Juvenile myoclonic epilepsy (3)	2 + 1*/3 * generalised slow wave bursts & occasional spikes	2/3	0/3
	Epilepsy with grand mal seizures on awakening (2)	2/2	0/2	1/2
	Photosensitive ep (1)	1/1	1/1	0/1
	Other (2)	2/2	0/2	2/2
Cryptogenic symptomatic generalised (2)		2/2	1/2	0/2 Both abnormal background
LOCALISATION RELATED (6)		0/6	0/6	3/6
UNDETERMINED (4)				
Both generalised & focal features (1)		1/1	0/1	0/1
Without unequivocal generalised or focal features (3)		0/2 (one not done)	0/2 (one not done)	0/2 (one not done)

4.2.3.2 Circumstance of Death in SUDEP Cases

Deaths occurred in sleep in at least 10 of 20 SUDEP cases (2 uncertain). Two people (both with primary generalised epilepsy) died while viewing a Video Display Unit. Both had had seizures in similar circumstances, one exclusively, and both had photosensitivity on EEG. One had reportedly never been treated and had a history of 4 previous generalised attacks only in similar circumstances, the other had discontinued medication independently a few weeks before death. In 3/20 cases the person died face down into the pillow and in 3 further cases the position of the head was likely to compromise breathing. These 6 cases were more likely to have internal or external petechial haemorrhages mentioned in the post-mortem report (table 19). This has to be interpreted cautiously. Pathologists may not always look for or record such findings and may be more likely to do so if the history is suggestive. Furthermore such changes may be more likely if resuscitation is attempted. In 2 further cases details regarding the exact position in which the body was found were incomplete. In one of these the coroner's officer's report states that the position of the head was 'possibly blocking the airway'.

Table 19: Interviews, Petechiae & Possible Suffocation

	Petechial Haemorrhages		
Possible Suffocation	Yes	No	Unknown
Yes	5	1	0
No	2	8	2
Unknown	2	0	0

p< 0.05 (Fisher's exact test)

Post-mortem findings in the 20 SUDEP cases included variable congestion of organs most commonly the lungs. In one case the bronchi were "virtually occluded by mucoid material". Toxicology had been performed in at least 8 cases. Certified causes of death are listed in table 20 with epilepsy not mentioned in only 2 cases.

Table 20: Interviews, Death Certificates in 20 SUDEP Cases

Status Epilepticus	7
Epilepsy/Chronic Epilepsy/Epileptic attack (mechanism not offered)	7
Unascertained	2
Sudden unexpected Death in Epilepsy	1
Epileptic seizure with mechanism proposed (asphyxia, respiratory inhalation of bronchial secretions cerebral ischaemia secondary to hypotension)	3

Only 1 terminal event of the SUDEP group was witnessed. The person got up within five minutes of a witnessed TCS and collapsed with no further convulsive movements. In unwitnessed cases, evidence indicative or suggestive of a seizure was found in 16/19 cases (table 20). Such evidence included tongue/lip biting (5), bruised tongue (1), complete or partial fall off bed (5), micturition (4), face contorted as in a seizure (2), and timing/situation as in habitual seizure (6). Such evidence is clearly not always conclusive.

Table 21: Interviews, Evidence for Seizure, 20 SUDEP Cases

1	Bitten tongue Incontinent of urine
2	Bitten tongue & lip
3	Bitten tongue Disrupted environment Fallen off bed
4	Died a.m. soon after waking Vast majority of habitual seizures at same time
5	Died early a.m. after waking Vast majority of habitual seizures at same time
6	Died while watching video - photosensitive Previous convulsions only in similar circumstances
8	Fall off bed Incontinent of urine - bruised tip of tongue
10	Died a.m. soon after waking after a late night out; JME; vast majority of seizures at the same time
11	Incontinent of urine
12	Fall off bed
13	No evidence (?)- disrupted environment:fall off chair
14	Incontinent of urine Pink/blood-stained secretions on pillow
17	Contorted facial expression 'as in a seizure'
18	Bitten tongue Computer game on - known photosensitivity
19	Witnessed seizure just before death
22	Fall off bed Facial expression 'as in a seizure'
23	Bitten lip Secretions
24	Fall off bed Nocturnal attacks only
25	No evidence
26	No evidence

Resuscitation was attempted in 6/20 SUDEP cases with a further 2 having mouth to mouth resuscitation only attempted by a relative. Among the six cases, only 2 had petechial haemorrhages mentioned in the post-mortem report.

Estimated total lifetime TCS in 20 cases were as follows: 5 had less than 10, 9 had between 10 and 100, and 5 had greater than 100 (1 unknown with no TCS reported for over 20 years). Seizure control as judged by frequency of TCS is shown in table 22. Only 1 patient was considered in remission and in this case medication was being withdrawn. Only five patients had a previous history of status epilepticus or of serial seizures requiring admission.

Table 22: Interviews, Tonic Clonic Seizures & SUDEP

More or equal to 1/day	none
More or equal to 1/week	3
More or equal to 1/month	8
More or equal to 1/three months	6
More or equal to 1/per year	3
More or equal to 1/five years	1+
Less than 1/five years	1*
Unknown	1

+ = Rx being withdrawn
* = Minor seizures greater than once every three months

Two patient had never been treated, and as already referred to, 1 patient had independently discontinued medication and in another medication was being withdrawn. Patients were on 0-3 antiepileptic drugs (mean 1.75) including acetazolamide (1), carbamazepine (12), ethosuximide (1), lamotrigine (3), phenobarbitone (1), phenytoin (8), primidone (2), valproate (7) and vigabatrin (2). Compliance was reported to be good in 16/18 treated individuals (one unknown). In 4 there had been a recent medication change during the month preceding death. One patient had omitted one dose 3 days before death. In a further patient, death occurred during the change-over period between one antiepileptic agent and another instituted because partial seizures were uncontrolled; in this case one witnessed generalised tonic clonic seizure occurred for the first time in 10 months the evening before an unwitnessed nocturnal death. Fatigue/sleep deprivation was considered a significant factor in another person with uncontrolled juvenile myoclonic epilepsy.

Of the patients classified as having primary generalised epilepsy, only 3/8 were on valproate at the time of death. Two patients had previously responded to valproate; in one of these it was withdrawn because of thrombocytopaenia. Of the remaining three patients, one had never been treated, one had only ever been treated with carbamazepine, and one had only ever been treated with phenytoin. Both the last-mentioned patients had generalised tonic clonic seizures on awakening and had

continued to have occasional seizures despite treatment. The patient on phenytoin had concealed this having chosen to continue driving. He died soon after getting up one morning.

There were additional factors that may have been relevant in individual cases. One person with post-traumatic epilepsy and severe facial injury requiring repeated major reconstructive surgery had previously expressed worries that breathing was compromised during seizures given small airways and facial deformity. Another person with asthma had been resuscitated in a near-miss event 4 years previously. One person had post-mortem evidence of a recent head injury 1 week or so before death, although this was not thought to be the cause of death.

4.3 Ictal Cardiorespiratory Parameters

Of 33 patients, one declined to participate and a further 3 patients agreed then withdrew. One other patient had cardiorespiratory recordings as part of assessment of suspected apnoeic spells distinct from his epileptic seizures. Only his epileptic seizures were analyzed. Seventeen patients had 47 clinical seizures recorded with additional cardiorespiratory parameters. Auras or pure electrographic seizures were not analyzed.

4.3.1 Patient Details

Thirteen cases underwent telemetry for presurgical assessment and 4 for diagnostic reasons. Mean age of the 17 patients (11 M, 6 F) was 32 years (range 18-43). Patient details and seizures types recorded are listed in table 22. These included 3 secondary generalised tonic clonic (TCS), 35 complex partial seizures (CPS), one spontaneous absence and 8 predominantly tonic seizures. The syndromic diagnosis and seizure types were based on clinical presentation, radiology (CT or MRI), pathology where available, EEG findings and features of the seizure on videorecording. In general patients showed the same pattern when more than one seizure was recorded. Only minor reductions in AED were instituted in some patients as shown in table 23.

Table 23: Ictal Recordings, Patient Details & Seizure Types

No	Sex	Age	Age at Onset (yrs)	Seizure Type Recorded (n)	Rx Reduced	Diagnosis
1	M	25	16	CPS (6)	Yes	LOCALISATION RELATED LT TEMPORAL LOBE SEIZURES
2*#	F	29	21	TCS (1)	Yes	LOCALISATION RELATED TEMPORAL LOBE SEIZURE - DISCORDANT DATA RE LATERALISATION
3*#+	F	25	5	CPS (1)	NO	LOCALISATION RELATED LT TEMPORAL LOBE SEIZURE
4*#+	M	40	7	TCS (2)	NO	LOCALISATION RELATED LT HEMISPHERE (EXTRATEMPORAL) SEIZURES
5+	F	27	4	CPS (2)	NO	LOCALISATION RELATED FRONTAL LOBE SEIZURES (PROBABLY LT)
6	M	18	8	CPS (2)	NO	LOCALISATION RELATED LT TEMPORAL LOBE SEIZURES
7	M	39	1	CPS (1)	NO	LOCALISATION RELATED LT HEMISPHERE
8	F	43	15	CPS (7)	YES	LOCALISATION RELATED LT TEMPORAL LOBE SEIZURES
9*	M	25	6	CPS (3)	YES	LOCALISATION RELATED LT TEMPORAL LOBE SEIZURES
10*^	M	27	0	MAINLY TONIC +/- CLONIC MOVEMENTS (8)	NO	SYMPTOMATIC GENERALISED
11	F	34	0	ABSENCE (1)	NO	SYMPTOMATIC GENERALISED SPONTANEOUS & SELF-INDUCED ABSENCES
12*	M	34	18	CPS (3)	YES	LOCALISATION RELATED DISCORDANT DATA; PROBABLE RT TEMPORAL LOBE SEIZURES
13	M	38	13	CPS (1)	NO	LOCALISATION RELATED LT TEMPORAL LOBE SEIZURE
14*	F	30	14	CPS (1)	NO	LOCALISATION RELATED ? LATERALISATION ON EEG
15*	M	30	24	CPS (6)	NO	LOCALISATION RELATED FRONTAL LOBE SEIZURES ? LATERALISATION
16*+	M	39	15	CPS (1)	YES	LOCALISATION RELATED TEMPORAL LOBE SEIZURE ? LATERALISATION
17*	M	36	12	CPS (1)	NO	LOCALISATION RELATED LT TEMPORAL LOBE SEIZURE

Central apnoea *

Obstructive apnoea #

Bradycardia +

Relative bradycardia ^

4.3 EEG Changes During Seizures

EEG changes during seizures were as follows: in 6 seizures (1 patient) there was no definite change, in 5 seizures (3 patients) there were nonspecific changes usually slowing of background rhythm, in 27 seizures (11 patients) there were clear rhythmic discharges, in 1 seizure/patient a generalised spike-wave discharge and in 8 seizures (1 patient) there was a clear and consistent generalised attenuation of background rhythm.

4.3.3 Apnoea During Seizures

Information was not always available in every seizure from each of the rib, abdominal bands or airflow. The abdominal respitrace band in particular did not always record a clear signal in addition to occasional superimposed movement artefact. However, the quality of recordings in conjunction with the available sound and video recording of seizures was informative in all but one case. In only one patient (patient 13) who walked around the room in a confused fashion during his seizure was no assessment possible.

Apnoea, defined as greater than 10 seconds (s), was recorded in 3 secondary TCS (2 patients), 1 tonic seizure and 16 CPS (7 patients). Duration ranged from 10 to 63 with a mean of 24 s. Central apnoea was observed in all of the 10 patients. During one complex seizure (case 3) a period of central apnoea lasting

13 s, which was associated with bradycardia, was followed by obstructive apnoea with good respiratory effort recorded and little airflow. At that point the patient's head had slumped onto her chest as she was seated. Blood pressure was not recorded. After 14 s air-entry was clearly heard to restart on video and recorded with the airflow sensor (figure 6). In 2 of the 3 generalised seizures recorded, air flow was reduced as compared to respiratory effort during the postictal phase indicating an obstructive element (case 4 - figure 7).

Where it was possible to ascertain central apnoea occurred in expiration (14/20 seizures, 8/10 patients).

4.3.4 Bradycardia During Seizures

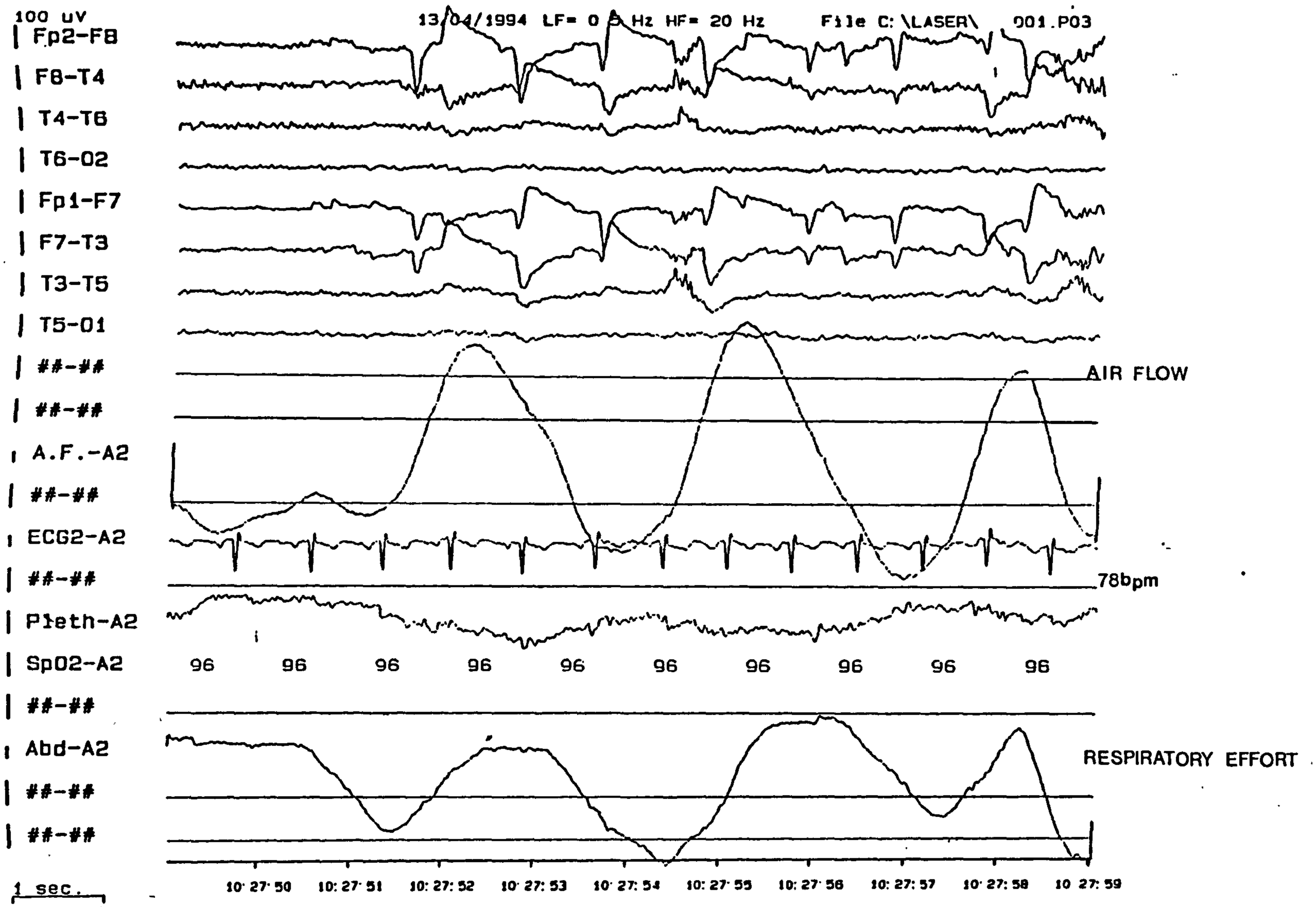
Bradycardia/ sinus arrest (maximum RR interval 2.8-8.6 s, mean 5.36) occurred in at least 4 patients (minimum 5 seizures). In three cases, one already described above, the bradycardia occurred within the context of apnoea, as shown in figures 6,7 & 8 (cases 3,4,16). In the fourth case bradycardia occurred soon after seizure onset at a time of altered respiratory pattern. The patient characteristically emitted a forceful moan interrupted by very brief inspirations. The vocalisation lasted for 18 s and was interrupted by about 10 very short inspirations.

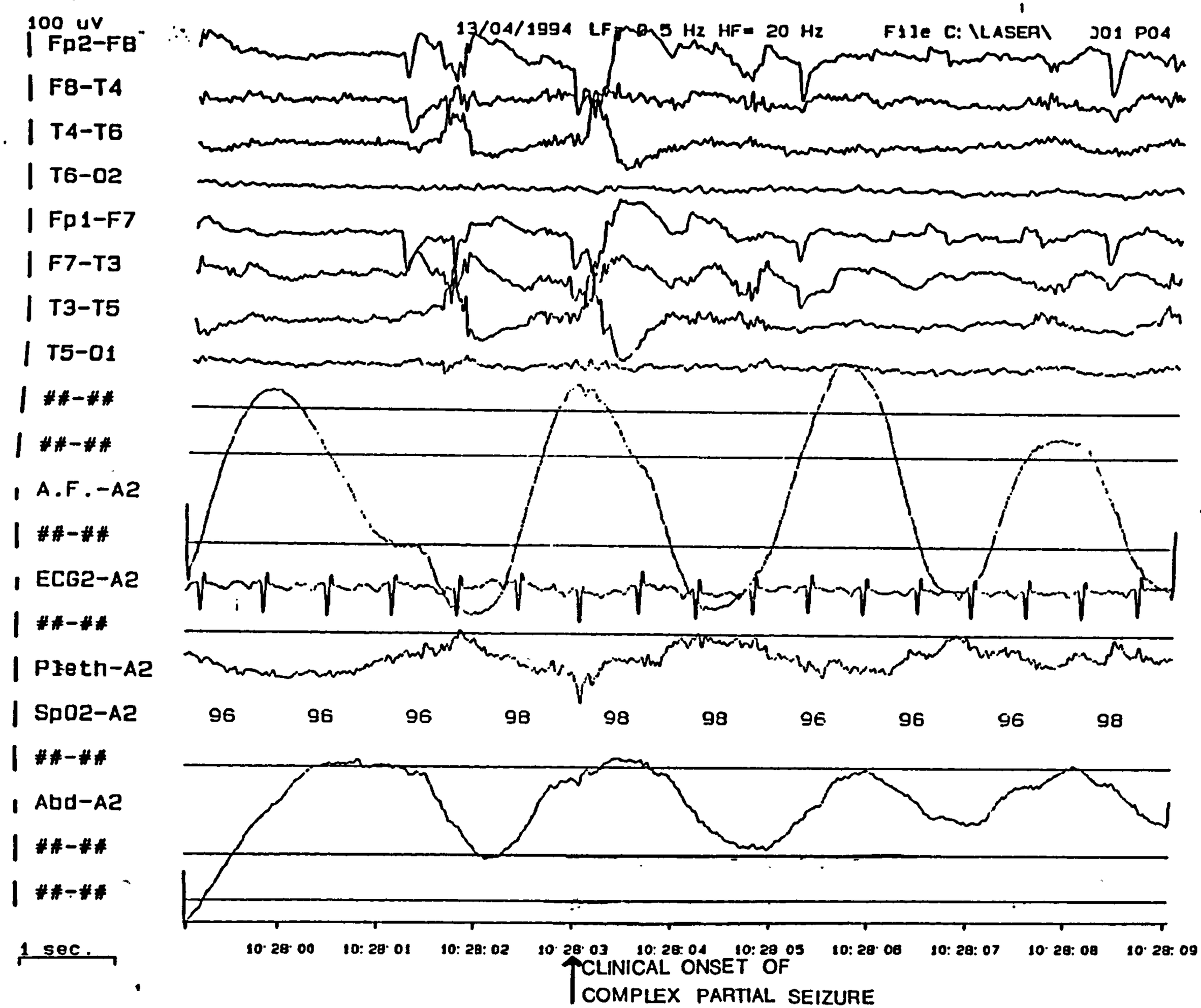
Lowest heart rates measured over 10 second epochs ranged from 6-42 with a mean of 26 bpm in 5 seizures.

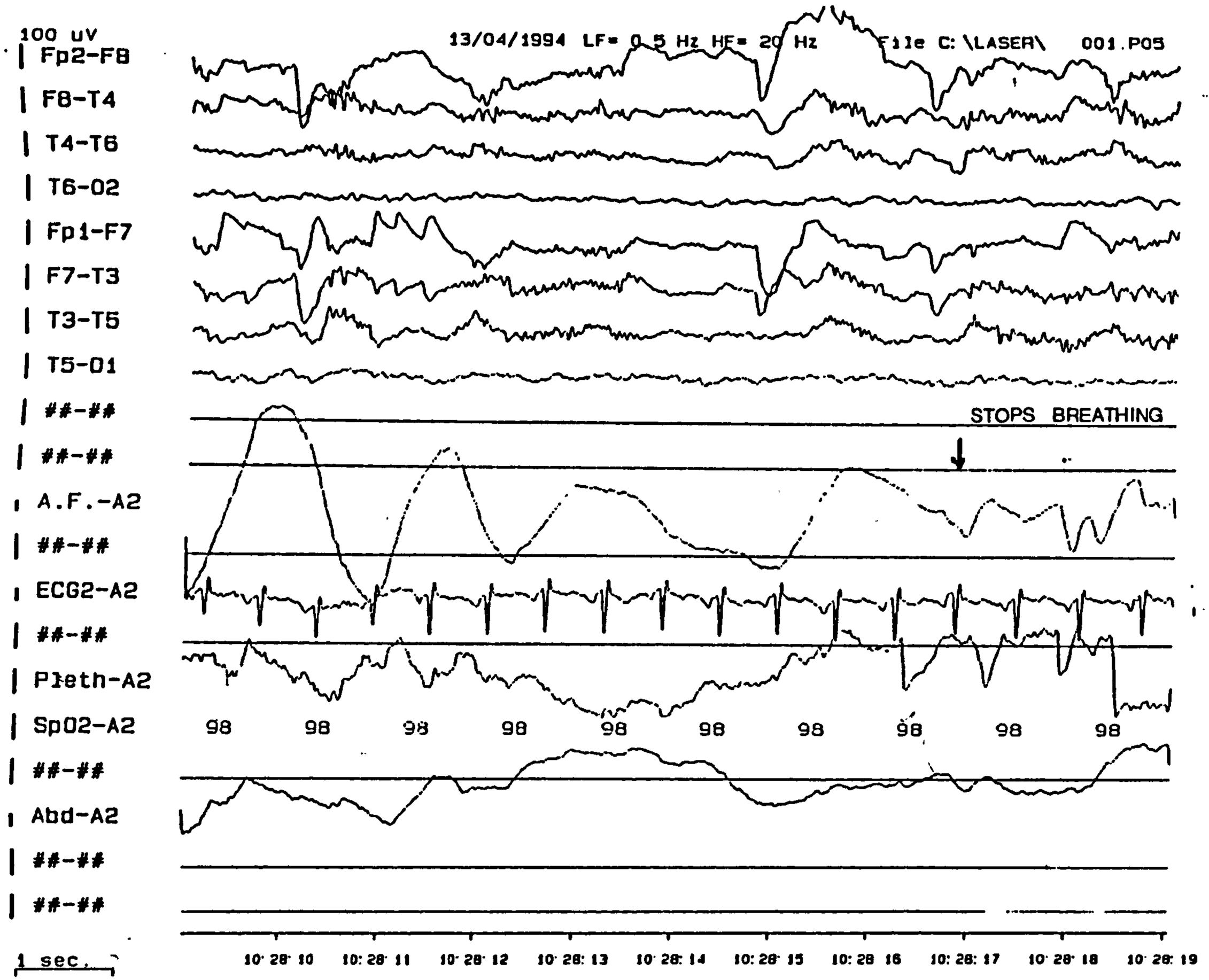
A further patient (case 10) had a relative bradycardia with a decrease in heart rate to 54 bpm during one of 8 tonic seizures only; although his respiration was frequently irregular during seizures, a decrease in heart rate of greater than 10 bpm occurred during one seizure associated with apnoea of just over 10 s in duration as shown in figure 9. This unusual patient with severe physical and mental handicap had two types of attacks: tonic seizures (with EEG change) as well as other unexplained periods of apnoea that were not associated with EEG changes. These apnoeic episodes were not included as seizures for the purpose of this study in view of their uncertain nature.

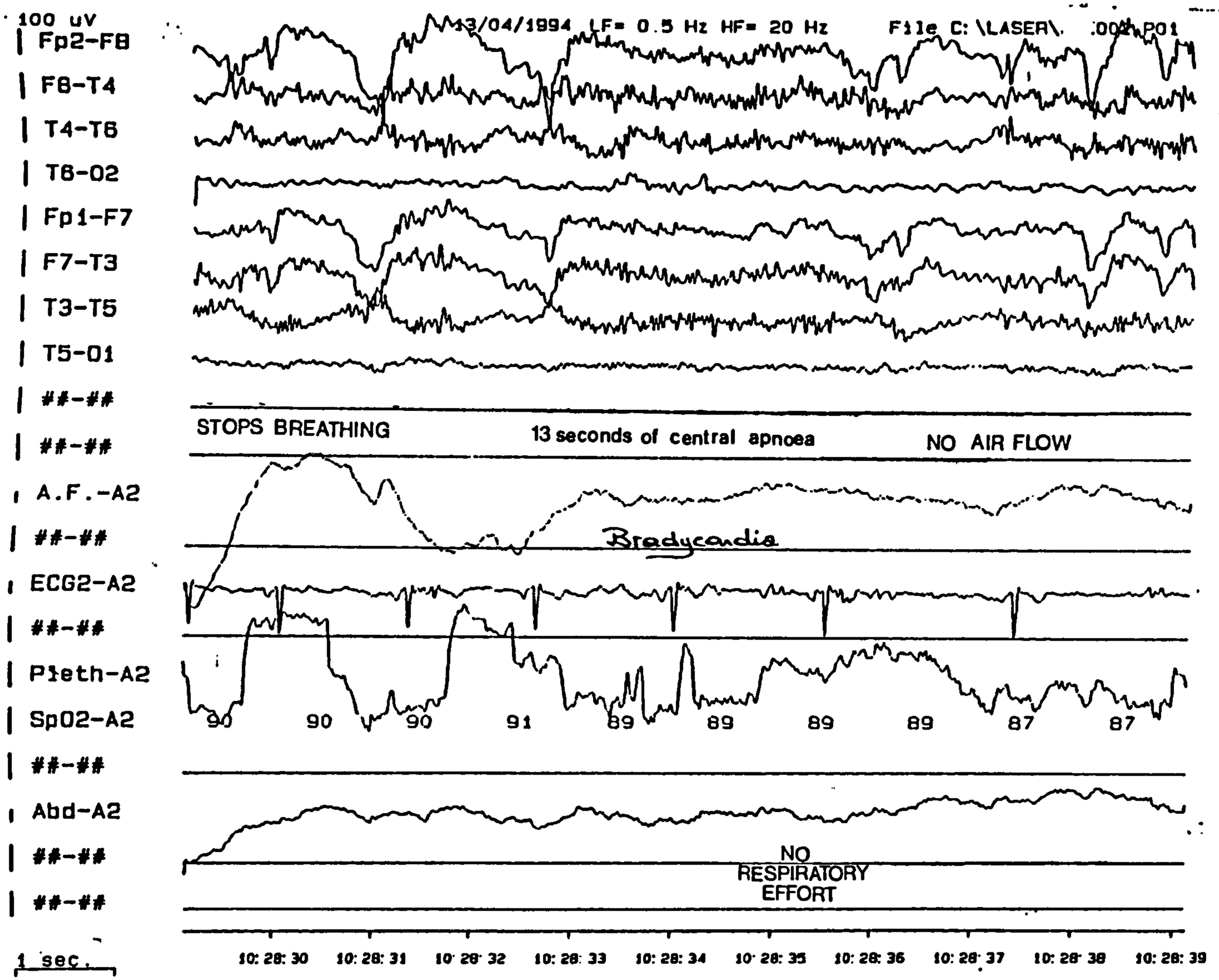
In a number of patients the ECG recording was sometimes obscured by muscle artefact. This did not usually represent any difficulty in terms of identifying tachycardias, which could still be ascertained between periods when the tracing was obscured, but could easily result in brief periods of bradycardia being missed. It was felt that in at least 7 patients (including the two with TCS) the ECG tracing was obscured sufficiently at critical times during seizures such transient bradycardia could not be excluded. In two of these patients, bradycardia was recorded in other seizures (figure 10, case 5).

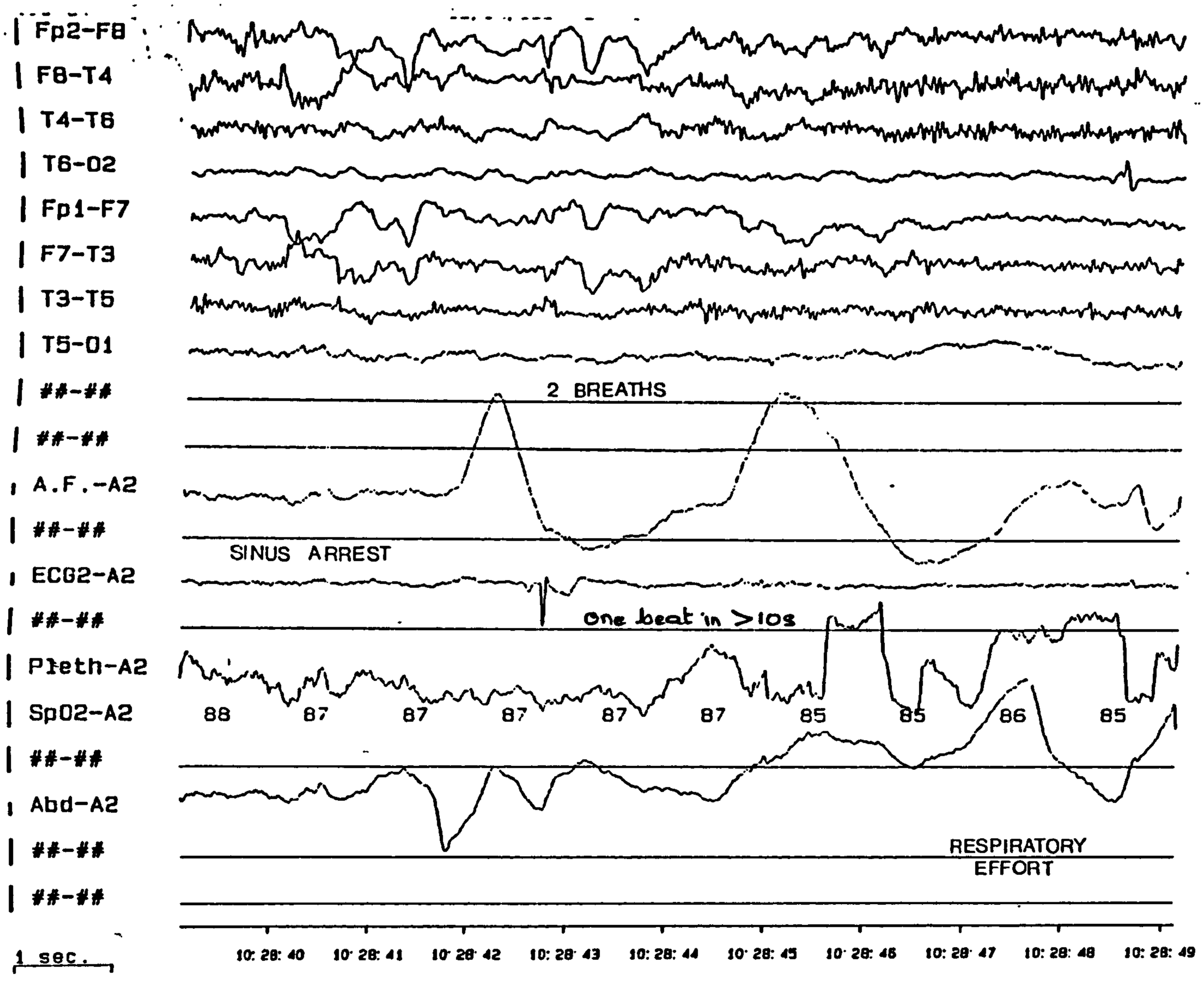
Figure 6: Case 3, Central & Obstructive Apnoea & Sinus Arrest - Complex Partial Seizure

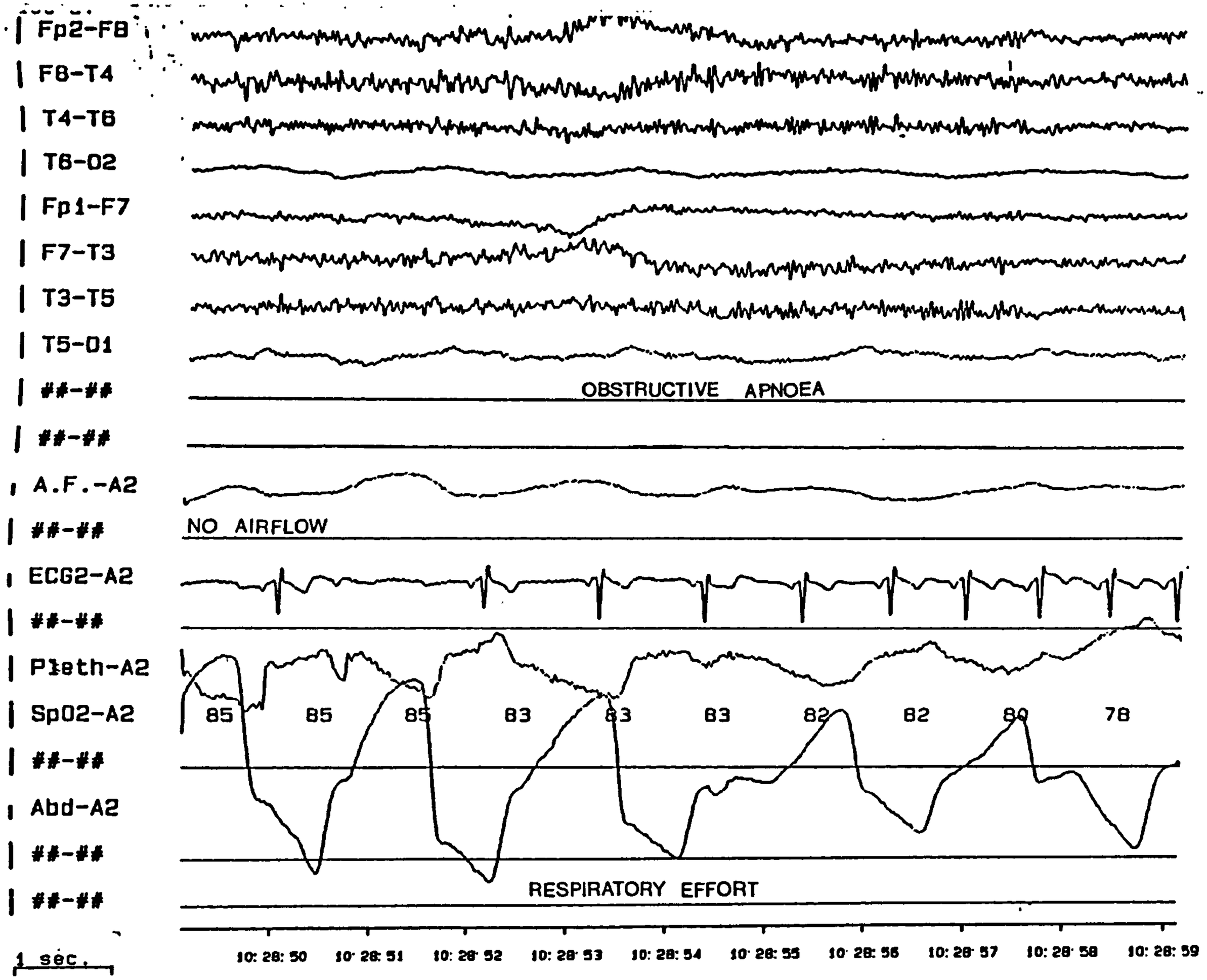

100 uV
13/04/1994 LF= 0.5 Hz HF= 20 Hz
File C:\LASER\ 001.P03
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
##-##
AIR FLOW
##-##
A.F.-A2
##-##
ECG2-A2
##-##
78bpm
Pleth-A2
SpO2-A2
96 96 96 96 96 96 96 96 96 96
##-##
Abd-A2
RESPIRATORY EFFORT
##-##
##-##
1 sec.
10:27:50 10:27:51 10:27:52 10:27:53 10:27:54 10:27:55 10:27:56 10:27:57 10:27:58 10:27:59

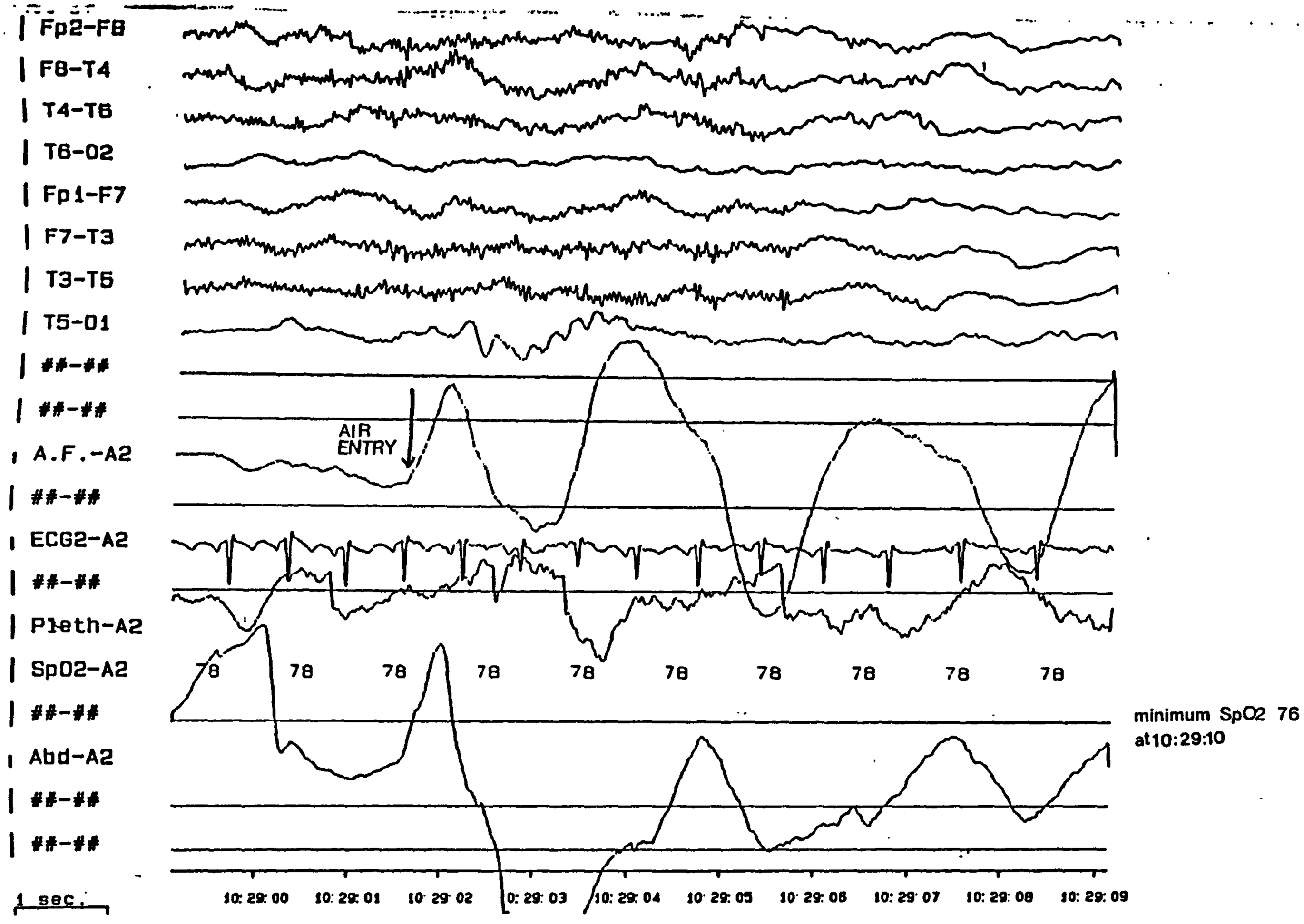

100 uV
13/04/1994 LF= 0.5 Hz HF= 20 Hz
File C:\LASER\ J01 P04
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
##-##
##-##
A.F.-A2
##-##
ECG2-A2
##-##
Pleth-A2
SpO2-A2
96 96 96 98 98 98 96 96 96 98
##-##
Abd-A2
##-##
##-##
1 sec.
10:28:00 10:28:01 10:28:02 10:28:03 10:28:04 10:28:05 10:28:06 10:28:07 10:28:08 10:28:09
CLINICAL ONSET OF
COMPLEX PARTIAL SEIZURE


100 uV
13/04/1994 LF= 0.5 Hz HF= 20 Hz File C:\LASER\ 001.P05
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
##-##
STOPS BREATHING
##-##
A.F.-A2
##-##
ECG2-A2
##-##
Pleth-A2
SpO2-A2
98 98 98 98 98 98 98 98 98 98
##-##
Abd-A2
##-##
##-##
1 sec.
10:28:10 10:28:11 10:28:12 10:28:13 10:28:14 10:28:15 10:28:16 10:28:17 10:28:18 10:28:19


100 uV
13/04/1994 LF= 0.5 Hz HF= 20 Hz
File C:\LASER\
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
##-##
##-##
STOPS BREATHING
13 seconds of central apnoea
NO AIR FLOW
A.F.-A2
##-##
Bradycardia
ECG2-A2
##-##
Pleth-A2
SpO2-A2
90 90 90 91 89 89 89 89 87 87
##-##
Abd-A2
##-##
NO
RESPIRATORY
EFFORT
##-##
1 sec.
10:28:30 10:28:31 10:28:32 10:28:33 10:28:34 10:28:35 10:28:36 10:28:37 10:28:38 10:28:39

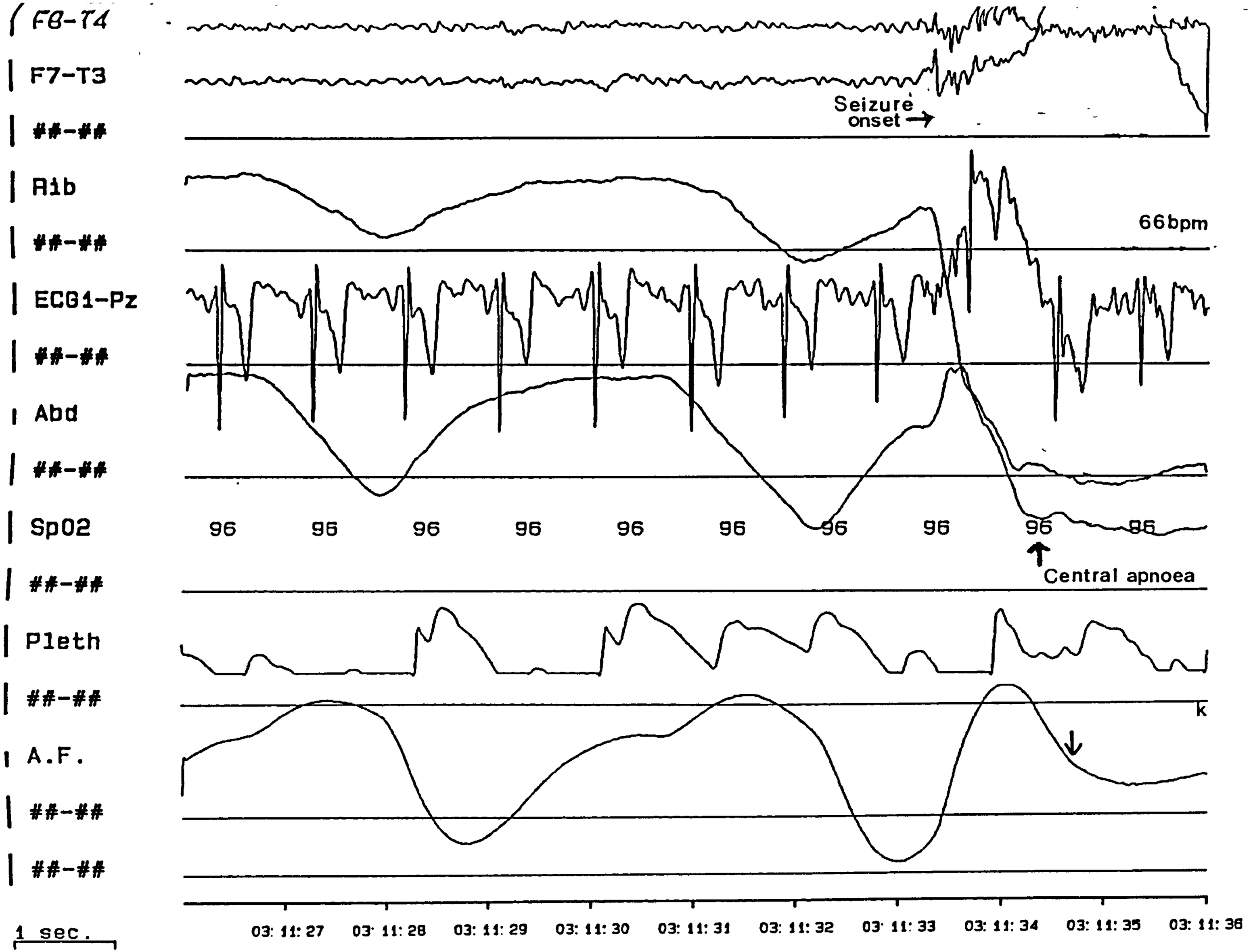

Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
##-##
2 BREATHS
##-##
A.F.-A2
##-##
SINUS ARREST
ECG2-A2
##-##
one beat in >10s
Pleth-A2
SpO2-A2
88 87 87 87 87 87 85 85 86 85
##-##
Abd-A2
##-##
RESPIRATORY EFFORT
##-##
1 sec.
10:28:40 10:28:41 10:28:42 10:28:43 10:28:44 10:28:45 10:28:46 10:28:47 10:28:48 10:28:49

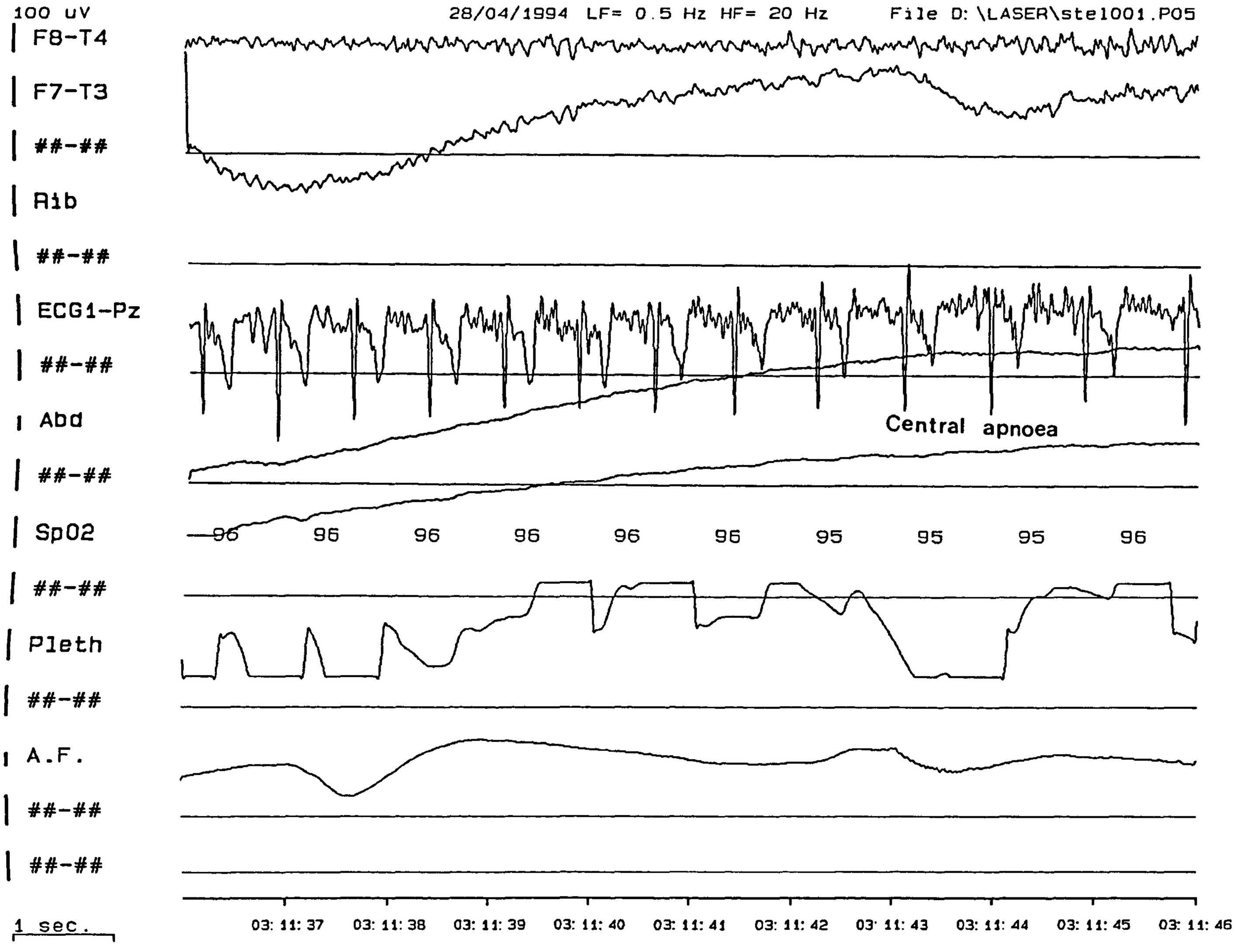

Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
##-##
OBSTRUCTIVE APNOEA
##-##
A.F.-A2
##-##
NO AIRFLOW
ECG2-A2
##-##
Pleth-A2
SpO2-A2
85
85
85
83
83
83
82
82
80
78
##-##
Abd-A2
##-##
##-##
RESPIRATORY EFFORT
1 sec.
10:28:50
10:28:51
10:28:52
10:28:53
10:28:54
10:28:55
10:28:56
10:28:57
10:28:58
10:28:59

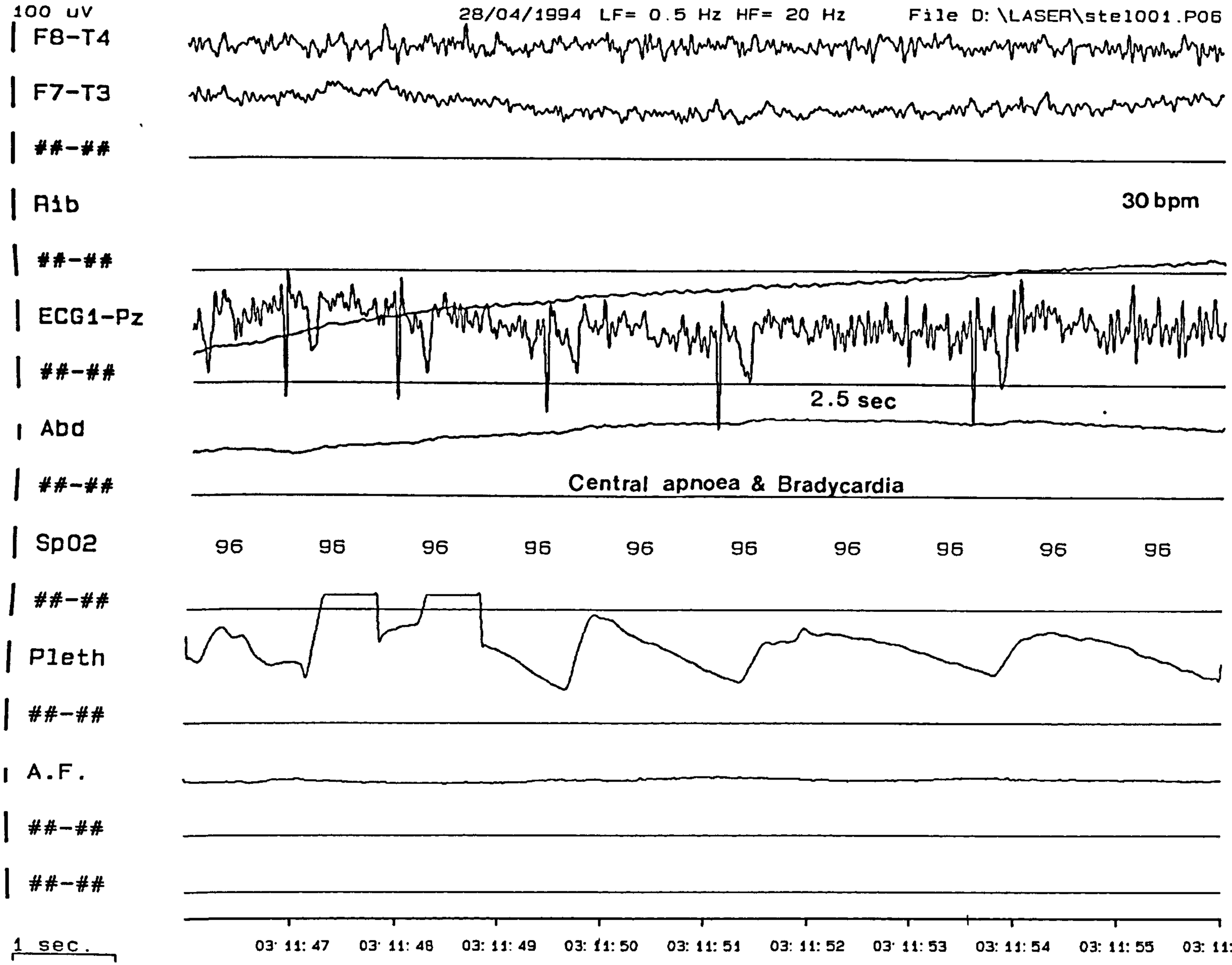


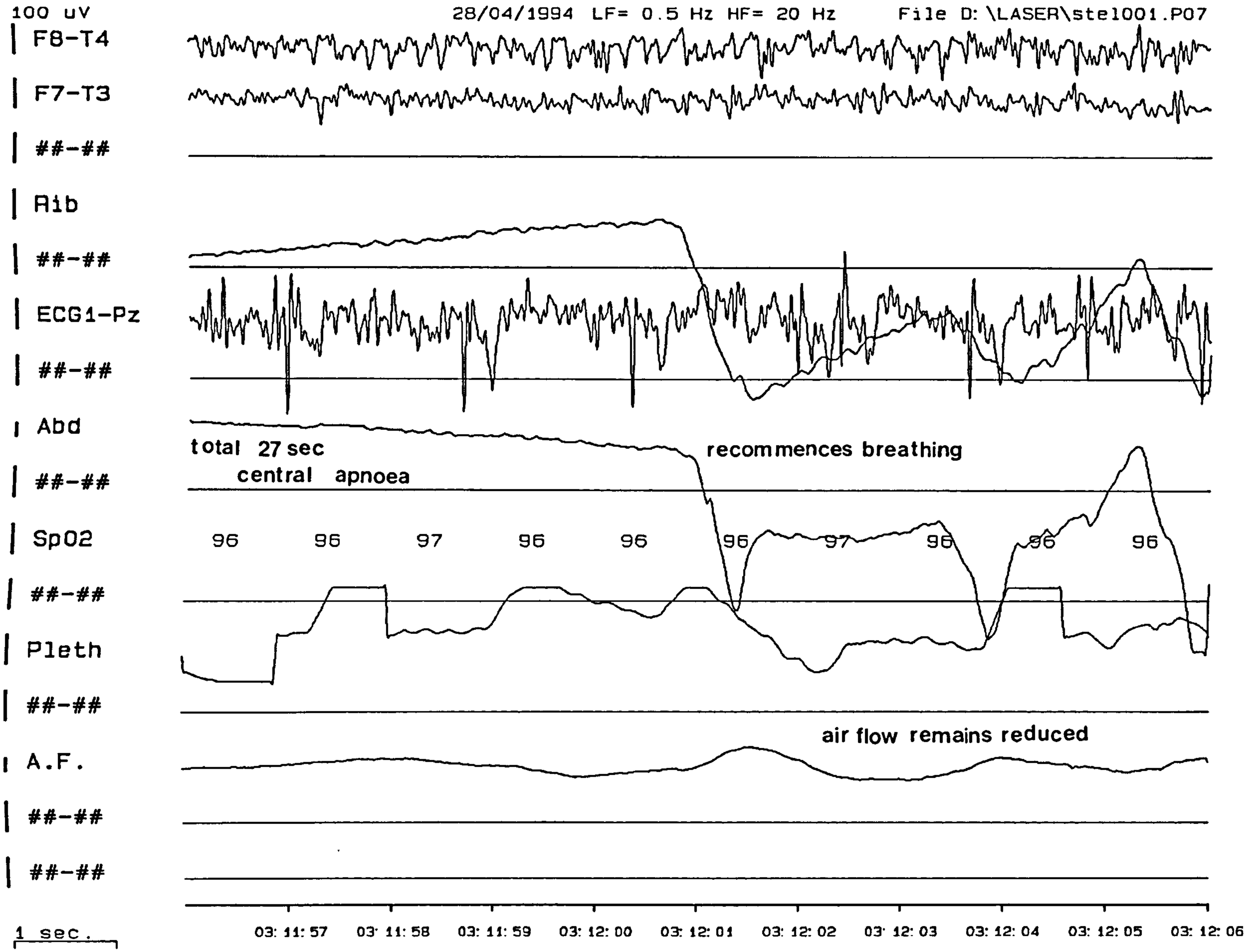
minimum SpO2 76
at10:29:10

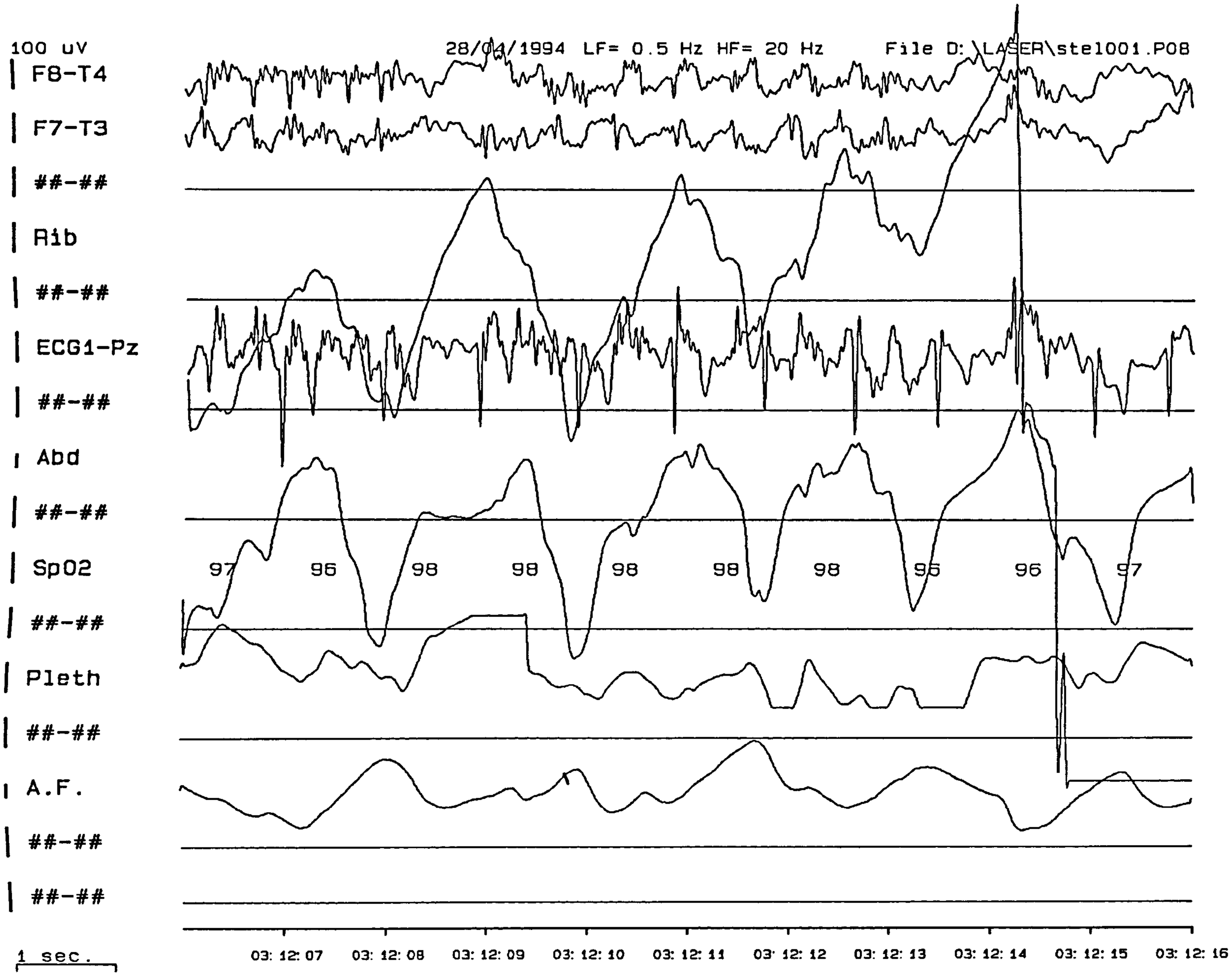
Figure 7: Case 4, Central & Obstructive Apnoea & Bradycardia Tonic Clonic Seizure

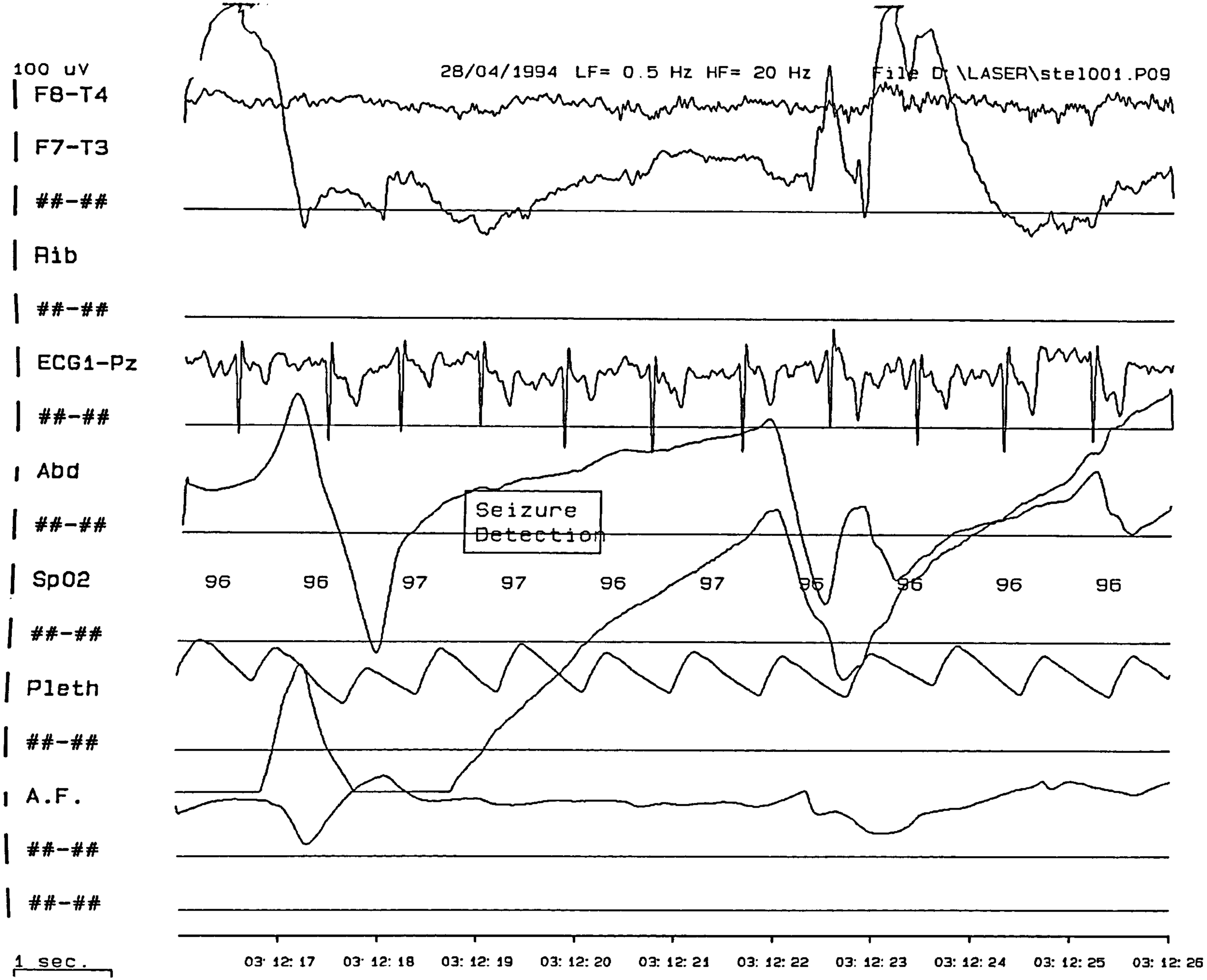

F8-T4
F7-T3
##-##
Seizure onset
Rib
##-##
66bpm
ECG1-Pz
##-##
Abd
##-##
Sp02
96
96
96
96
96
96
96
96
96
96
Central apnoea
##-##
Pleth
##-##
k
A.F.
##-##
##-##
1 sec.
03: 11: 27
03: 11: 28
03: 11: 29
03: 11: 30
03: 11: 31
03: 11: 32
03: 11: 33
03: 11: 34
03: 11: 35
03: 11: 36

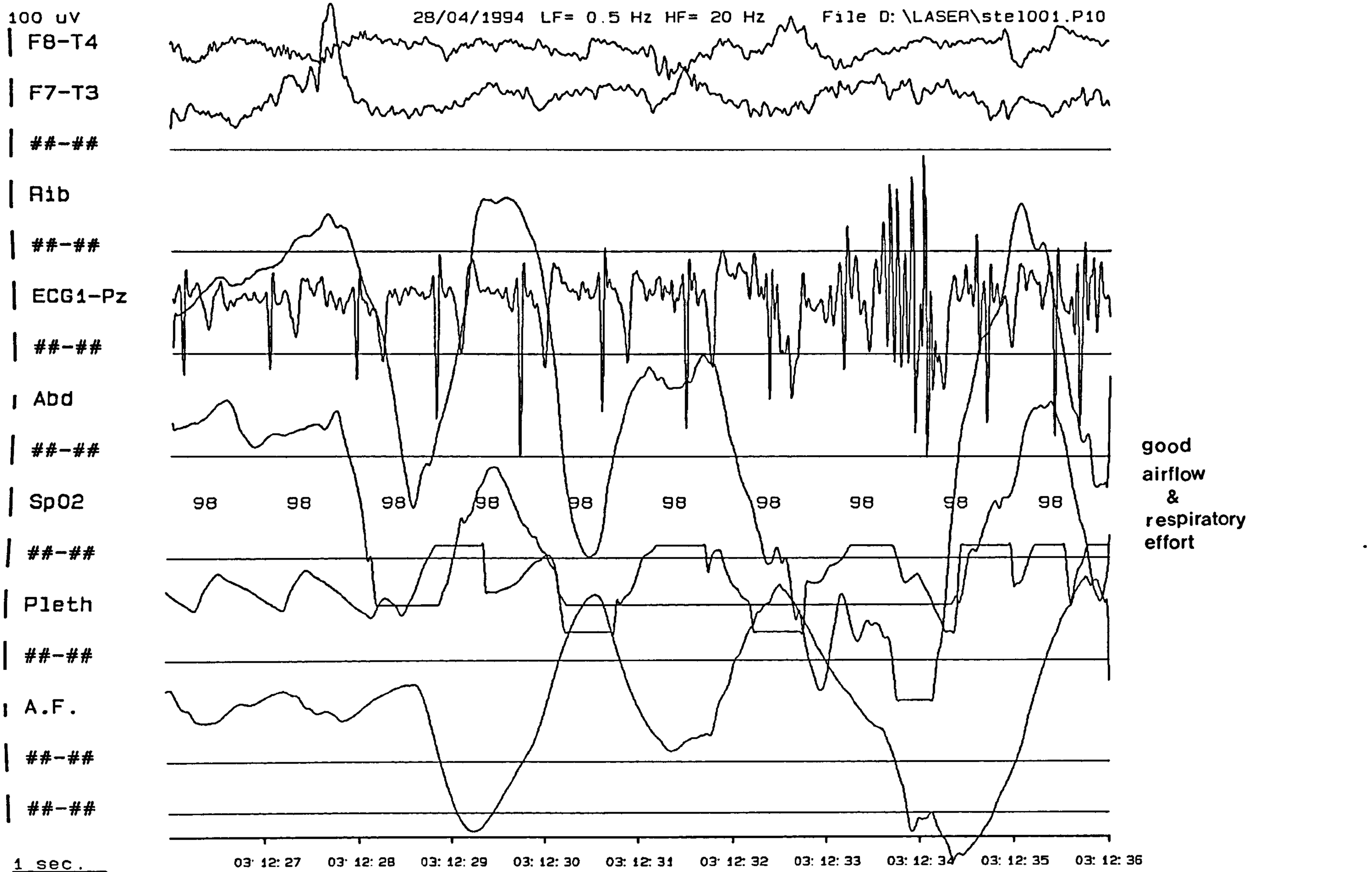

100 uV
28/04/1994 LF= 0.5 Hz HF= 20 Hz
File D:\LASER\ste1001.P05
F8-T4
F7-T3
##-##
Rib
##-##
ECG1-Pz
##-##
Abd
##-##
Central apnoea
SpO2
96 96 96 96 96 96 95 95 95 96
##-##
Pleth
##-##
A.F.
##-##
##-##
1 sec.
03:11:37 03:11:38 03:11:39 03:11:40 03:11:41 03:11:42 03:11:43 03:11:44 03:11:45 03:11:46

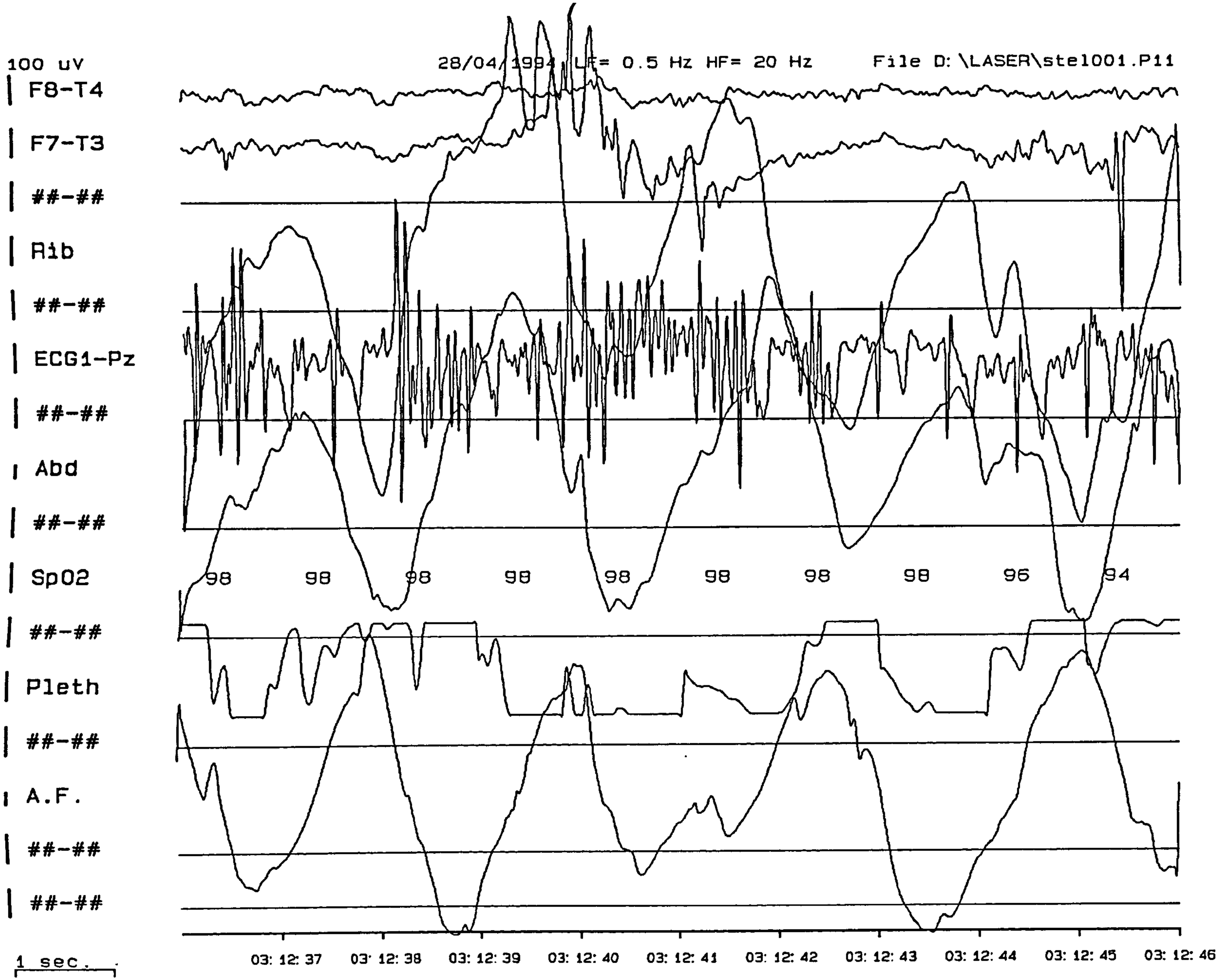

100 uV
28/04/1994 LF= 0.5 Hz HF= 20 Hz File D:\LASER\ste1001.P06
F8-T4
F7-T3
##-##
Rib
30 bpm
##-##
ECG1-Pz
##-##
2.5 sec
Abd
##-##
Central apnoea & Bradycardia
Sp02
96 96 96 96 96 96 96 96 96 96
##-##
Pleth
##-##
A.F.
##-##
##-##
1 sec.
03: 11: 47
03: 11: 48
03: 11: 49
03: 11: 50
03: 11: 51
03: 11: 52
03: 11: 53
03: 11: 54
03: 11: 55
03: 11: 56


100 uV
28/04/1994 LF= 0.5 Hz HF= 20 Hz File D:\LASER\ste1001.P07
F8-T4
F7-T3
##-##
Rib
##-##
ECG1-Pz
##-##
Abd
total 27 sec
central apnoea
recommences breathing
##-##
SpO2
96 96 97 96 96 96 97 96 96 96
##-##
Pleth
##-##
air flow remains reduced
A.F.
##-##
##-##
1 sec.
03:11:57 03:11:58 03:11:59 03:12:00 03:12:01 03:12:02 03:12:03 03:12:04 03:12:05 03:12:06


100 uV
28/04/1994 LF= 0.5 Hz HF= 20 Hz
File D:\LASER\ste1001.P08
F8-T4
F7-T3
##-##
Rib
##-##
ECG1-Pz
##-##
Abd
##-##
Sp02
97
96
98
98
98
98
98
96
96
97
##-##
Pleth
##-##
A.F.
##-##
##-##
1 sec.
03: 12: 07
03: 12: 08
03: 12: 09
03: 12: 10
03: 12: 11
03: 12: 12
03: 12: 13
03: 12: 14
03: 12: 15
03: 12: 16


100 uV
28/04/1994 LF= 0.5 Hz HF= 20 Hz
File D:\LASER\ste1001.P09
F8-T4
F7-T3
##-##
Rib
##-##
ECG1-Pz
##-##
Abd
##-##
Seizure Detection
SpO2
96
96
97
97
96
97
96
96
96
96
##-##
Pleth
##-##
A.F.
##-##
##-##
1 sec.
03: 12: 17
03: 12: 18
03: 12: 19
03: 12: 20
03: 12: 21
03: 12: 22
03: 12: 23
03: 12: 24
03: 12: 25
03: 12: 26


100 uV
28/04/1994 LF= 0.5 Hz HF= 20 Hz
File D:\LASER\ste1001.P10
F8-T4
F7-T3
##-##
Rib
##-##
ECG1-Pz
##-##
Abd
##-##
SpO2
98
98
98
98
98
98
98
98
98
98
##-##
Pleth
##-##
A.F.
##-##
##-##
1 sec.
03: 12: 27
03: 12: 28
03: 12: 29
03: 12: 30
03: 12: 31
03: 12: 32
03: 12: 33
03: 12: 34
03: 12: 35
03: 12: 36
good airflow & respiratory effort


100 uV
28/04/1994 LF= 0.5 Hz HF= 20 Hz File D:\LASER\ste1001.P11
F8-T4
F7-T3
##-##
Rib
##-##
ECG1-Pz
##-##
Abd
##-##
SpO2
98
98
98
98
98
98
98
98
96
94
##-##
Pleth
##-##
A.F.
##-##
##-##
1 sec.
03: 12: 37
03: 12: 38
03: 12: 39
03: 12: 40
03: 12: 41
03: 12: 42
03: 12: 43
03: 12: 44
03: 12: 45
03: 12: 46

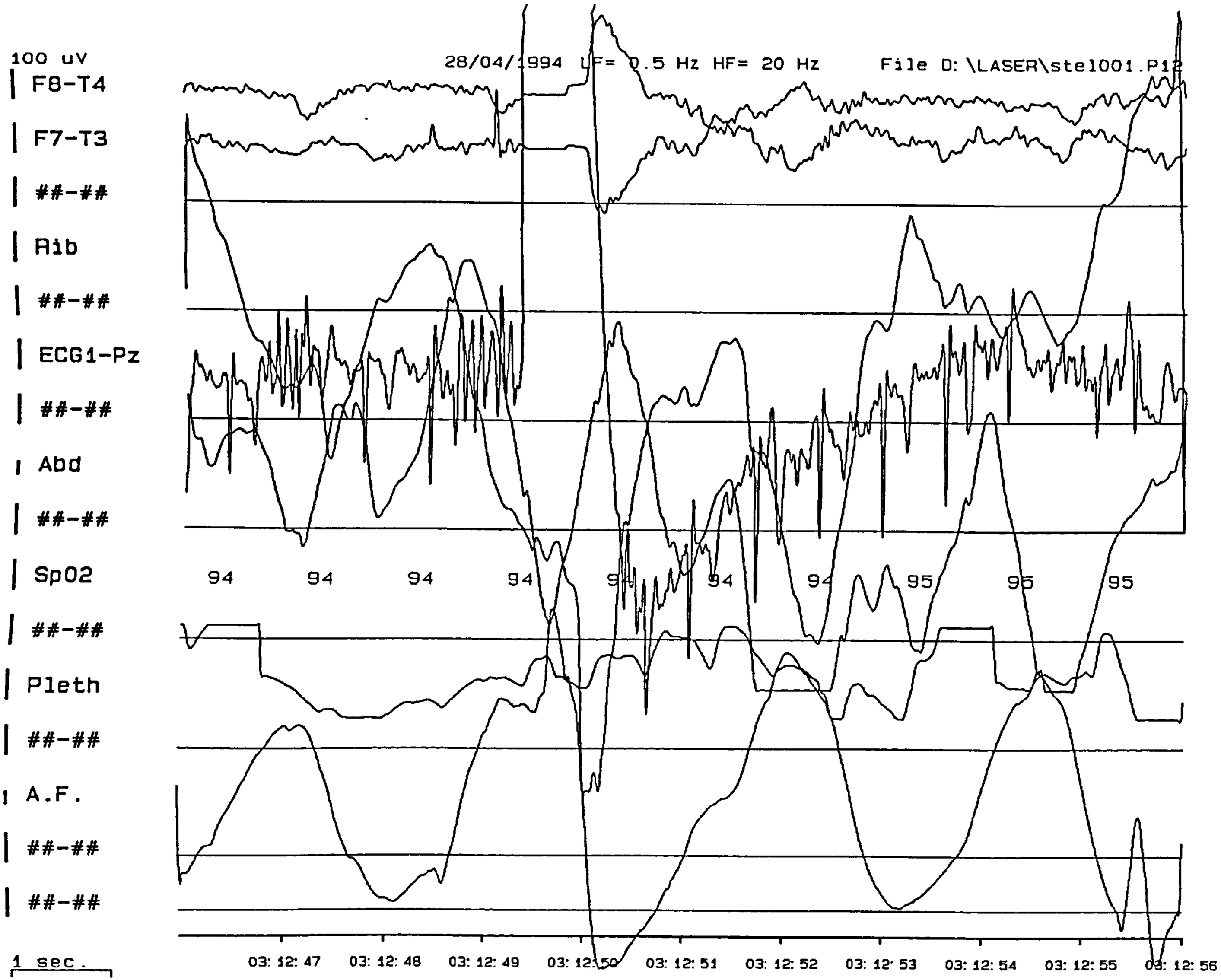
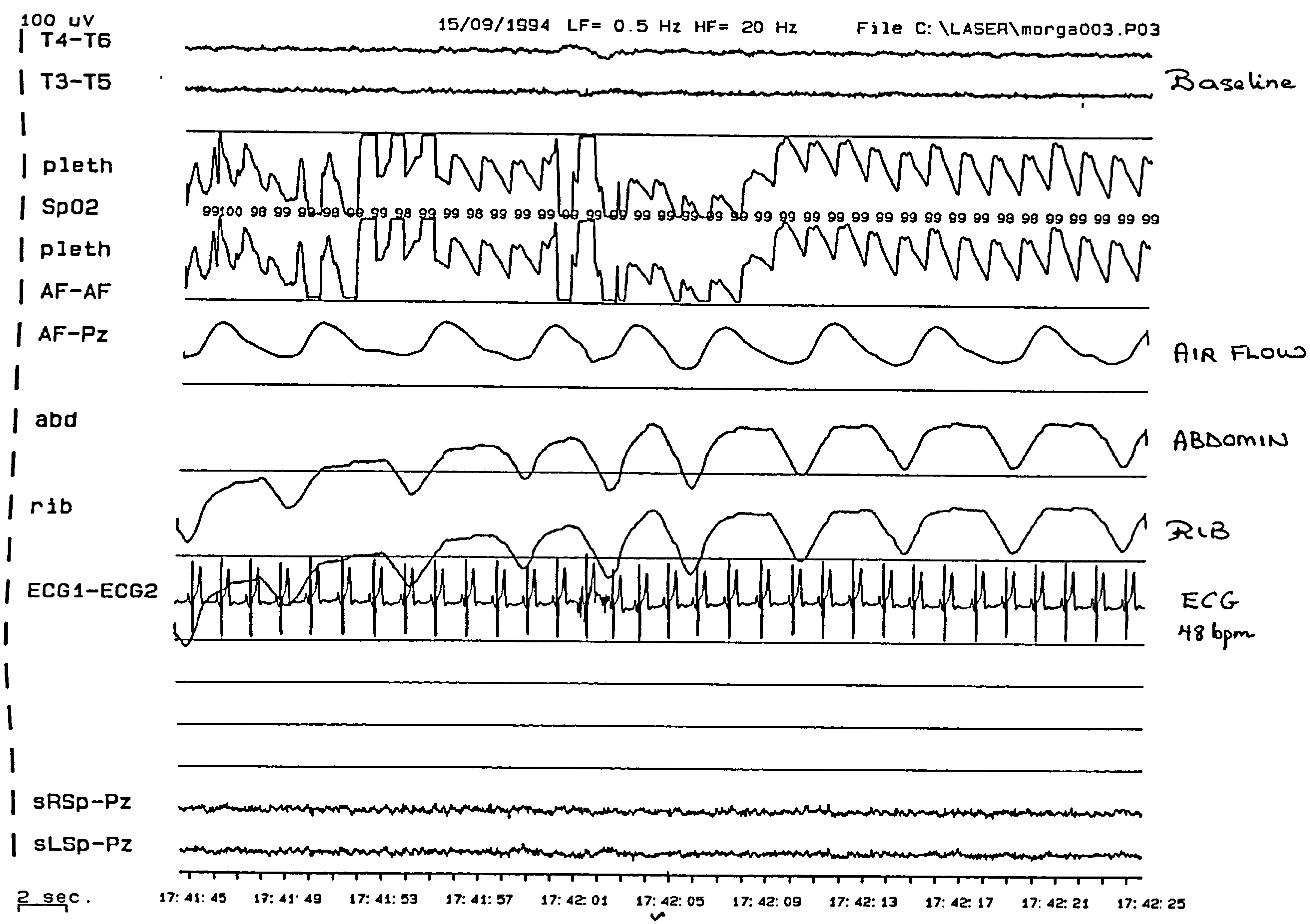

100 uV
28/04/1994 LF= 0.5 Hz HF= 20 Hz
File D:\LASER\ste1001.P12
F8-T4
F7-T3
##-##
Rib
##-##
ECG1-Pz
##-##
Abd
##-##
Sp02
94
94
94
94
94
94
94
95
95
95
##-##
Pleth
##-##
A.F.
##-##
##-##
1 sec.
03:12:47
03:12:48
03:12:49
03:12:50
03:12:51
03:12:52
03:12:53
03:12:54
03:12:55
03:12:56

Figure 8: Case 16, Central Apnoea & Bradycardia

Complex Partial Seizure


15/09/1994 LF= 0.5 Hz HF= 20 Hz
File C:\LASER\morga003.P03
100 uV
T4-T6
T3-T5
pleth
SpO2
pleth
AF-AF
AF-Pz
abd
rib
ECG1-ECG2
sRSp-Pz
sLSp-Pz
2 sec.
99100 98 99 98 98 99 99 98 99 99 98 99 99 99 99 99 99 99 99 99 99 99 99 99 99 99 99 99 99 99 99 98 98 99 99 99 99 99
17:41:45
17:41:49
17:41:53
17:41:57
17:42:01
17:42:05
17:42:09
17:42:13
17:42:17
17:42:21
17:42:25
Baseline
AIR FLOW
ABDOMIN
RIB
ECG
48 bpm

100 uV 15/09/1994 LF= 0.5 Hz HF= 10 Hz File D:\LASER\ 005.P01

T4-T6

T6-02

T3-T5

T5-01

55 bpm — 81 bpm — 99 bpm — 100 bpm

ECG1-ECG2

Push Button

SpO2

100 99 99 98 99 99 99 99 99 98 99 99 99 98 98 98 98 98 98 98 99 99 99 99 99 99 99 99 98 99 98 99 99 99 99 98

pleth

Irregular Breathing

Folds paper reaches for EB

AF-Pz

AIR.FLOW

Stares downwards

rib

RESPIRATORY EFFORT - RIB

COMPLEX PARTIAL SEIZURE

abd

ABDOMINAL TRACE - UNSATISFACTORY

CLINICAL ONSET

2 sec.

17:50:45 17:50:49 17:50:53 17:50:57 17:51:01 17:51:05 17:51:09 17:51:13 17:51:17 17:51:21 17:51:25

100 uV 15/09/1994 LF= 0.5 Hz HF= 10 Hz File D:\LASER\ 005.P02

T4-T6

T6-02

T3-T5

EEG ONSET

T5-01

128 bpm 93.5 bpm 102 bpm 60 bpm

ECG1-ECG2

Seizure Detection

SpO2 98 98 99 98 96 97 97 96 97 97 97 97 96 97 97 96 97 97 97 97 96 96 97 96 96 96 97 96 97 96 96 96 96 96 96 96 95 95 95 94 96

pleth

Irregular Breathing

AF-Pz

rib

says "mmm" repeatedly

mutters

abd

Starts fidgetting

sec. 17:51:25 17:51:29 17:51:33 17:51:37 17:51:41 17:51:45 17:51:49 17:51:53 17:51:57 17:52:01 17:52:05

100 uV

15/09/1994 LF= 0.5 Hz HF= 10 Hz File D:\LASER\ ...005.P03

T4-T6

T6-O2

T3-T5

T5-O1

40 bpm

26 bpm

26 bpm

60.5 bpm.

ECG1-ECG2

Clear bradycardia during apnoea

SpO2

95 94 94 95 95 95 95 95 95 95 95 95 95 94 95 94 95 94 94 95 95 94 95 94 94 95 95 95 95 95 95 95 95 95 94 95 95 94 94 95

pleth

Central Apnoea

Restarts Breathing

AF-Pz

Fumbles with EB with R hand

rib

abd

Stops fidgetting & mumbling

Still, stares downwards Starts rolling head side to side

2 sec

17:52:05 17:52:09 17:52:13 17:52:17 17:52:21 17:52:25 17:52:29 17:52:33 17:52:37 17:52:41 17:52:45

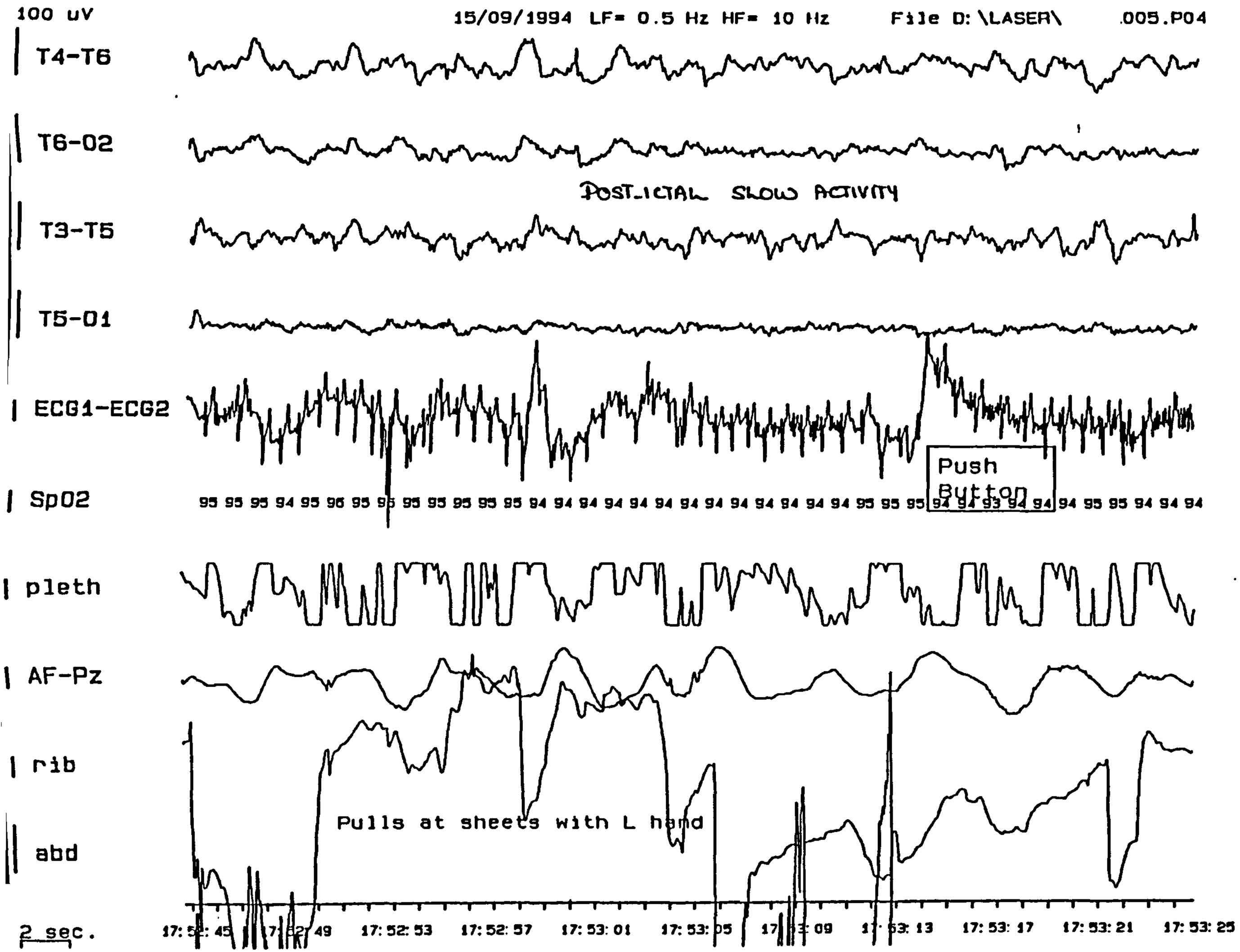
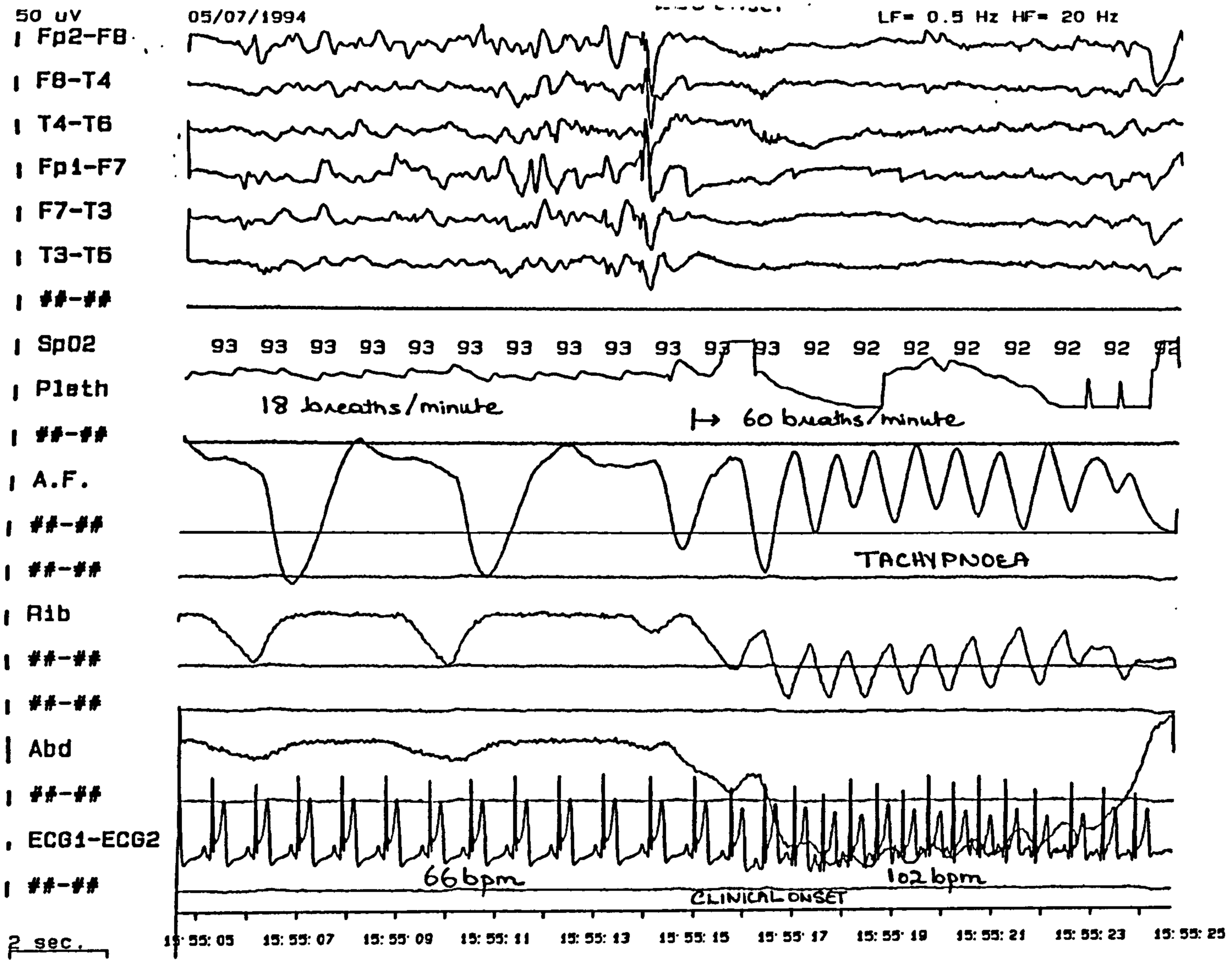
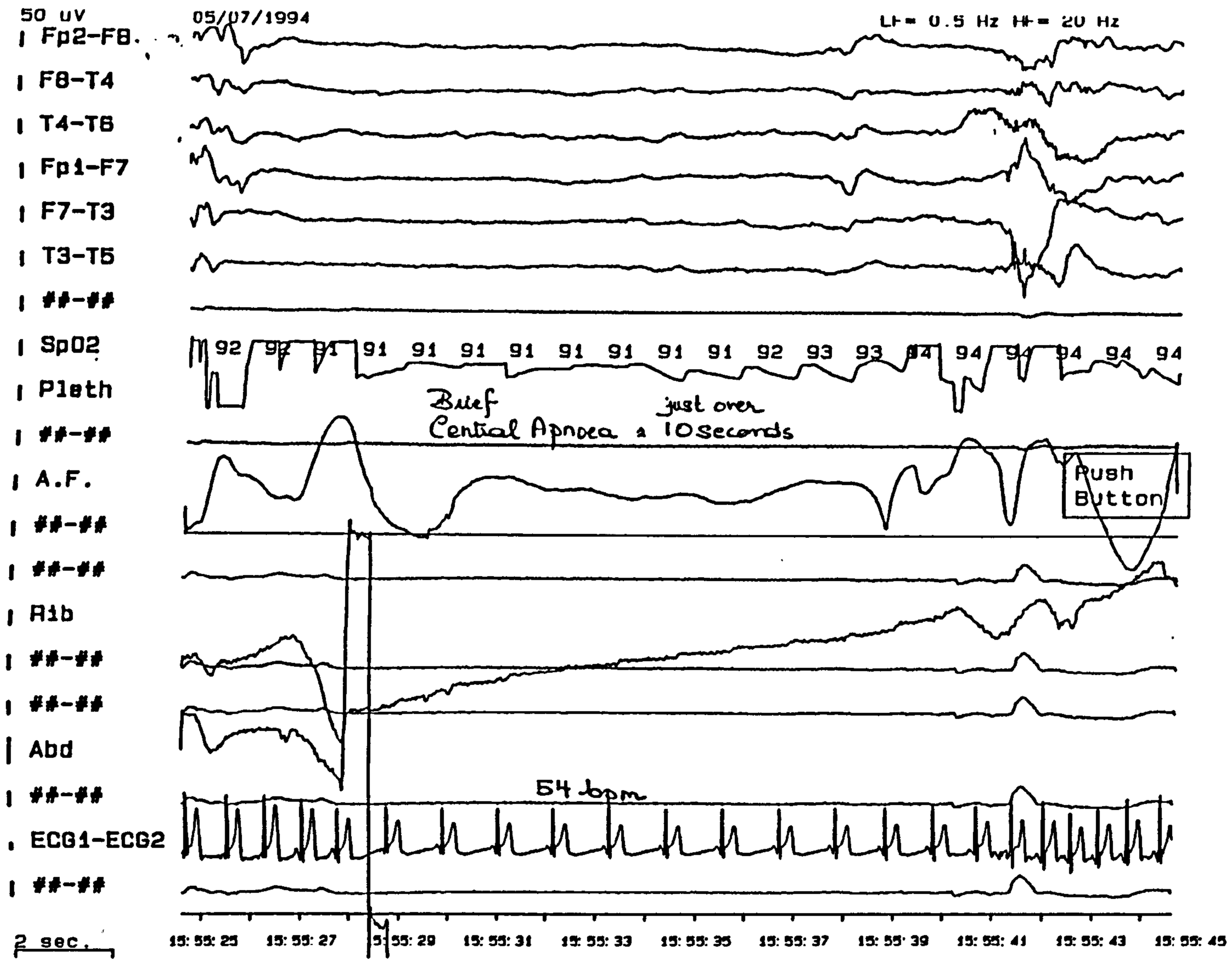

100 uV
15/09/1994 LF= 0.5 Hz HF= 10 Hz
File D:\LASER\
.005.P04
T4-T6
T6-O2
POST-ICTAL SLOW ACTIVITY
T3-T5
T5-O1
ECG1-ECG2
Push Button
SpO2
95 95 95 94 95 96 95 95 95 95 95 95 95 94 94 94 94 94 94 94 94 94 94 94 94 94 94 95 95 95 94 94 93 94 94 94 95 95 94 94 94
pleth
AF-Pz
rib
Pulls at sheets with L hand
abd
2 sec.
17:52:45
17:52:49
17:52:53
17:52:57
17:53:01
17:53:05
17:53:09
17:53:13
17:53:17
17:53:21
17:53:25

Figure 9: Case 10, Central Apnoea & Decrease in Heart Rate Tonic Seizure


50 uV
05/07/1994
LF= 0.5 Hz HF= 20 Hz
Fp2-F8
F8-T4
T4-T6
Fp1-F7
F7-T3
T3-T5
##-##
SpO2
93 93 93 93 93 93 93 93 93 93 93 92 92 92 92 92 92 92 92
Pleth
18 breaths/minute
60 breaths/minute
##-##
A.F.
##-##
##-##
TACHYPNOEA
Rib
##-##
##-##
Abd
##-##
ECG1-ECG2
66bpm
102bpm
##-##
CLINICAL ONSET
2 sec.
15:55:05
15:55:07
15:55:09
15:55:11
15:55:13
15:55:15
15:55:17
15:55:19
15:55:21
15:55:23
15:55:25


50 uV
05/07/1994
LF= 0.5 Hz HF= 20 Hz
Fp2-F8
F8-T4
T4-T6
Fp1-F7
F7-T3
T3-T5
##-##
SpO2
92 92 91 91 91 91 91 91 91 91 91 92 93 93 94 94 94 94 94 94
Pleth
Brief Central Apnoea just over 10seconds
##-##
A.F.
Push Button
##-##
##-##
Rib
##-##
##-##
Abd
##-##
54 bpm
ECG1-ECG2
##-##
2 sec.
15:55:25 15:55:27 15:55:29 15:55:31 15:55:33 15:55:35 15:55:37 15:55:39 15:55:41 15:55:43 15:55:45

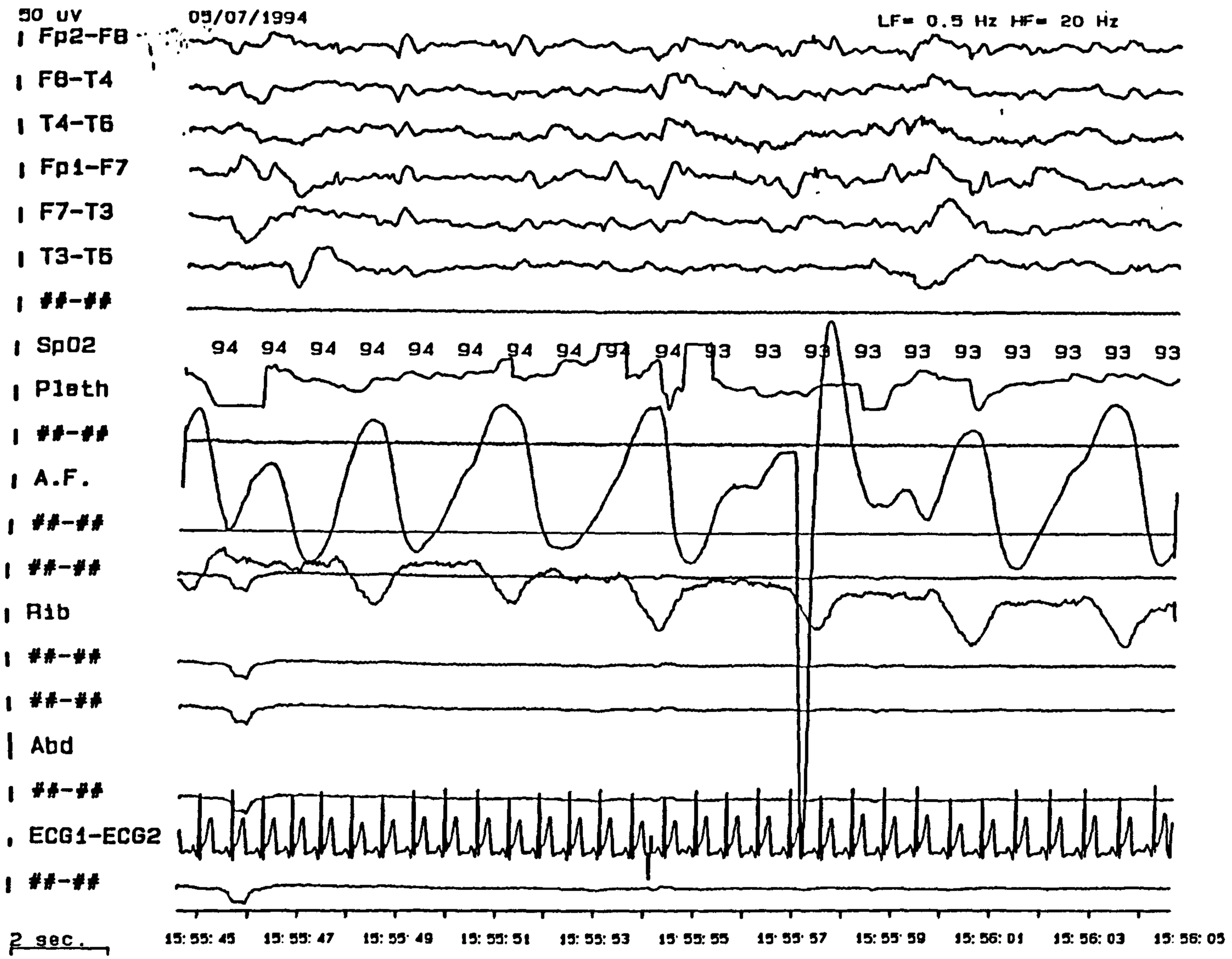
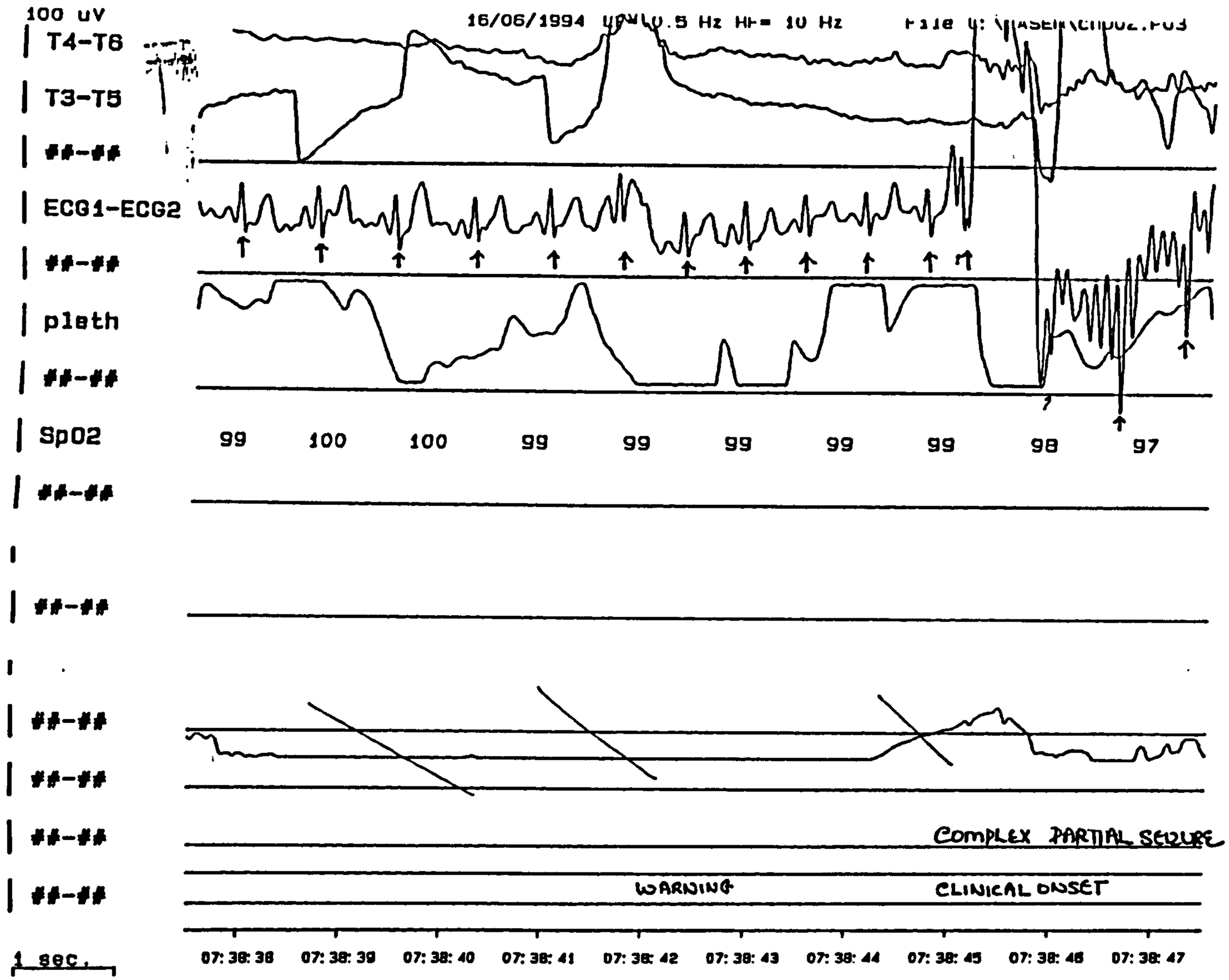
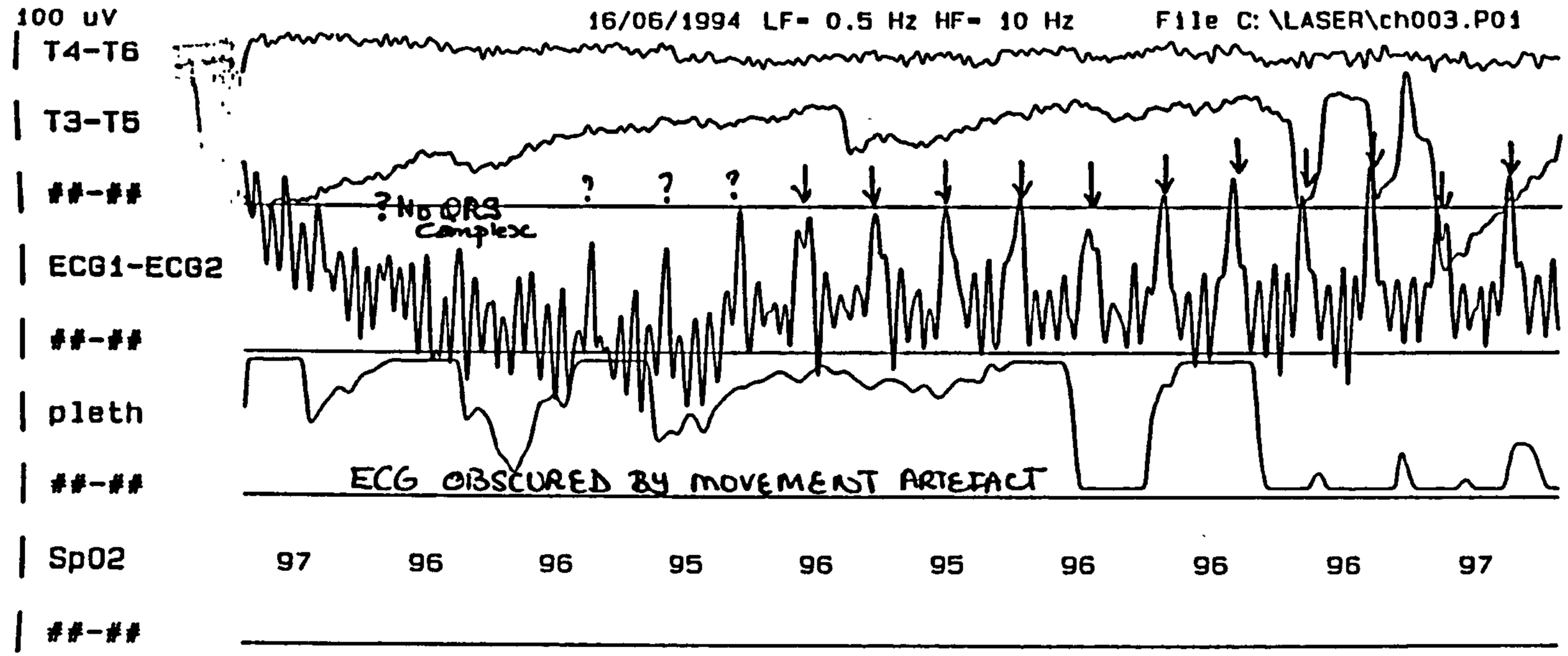

50 uV
05/07/1994
LF= 0.5 Hz HF= 20 Hz
Fp2-F8
F8-T4
T4-T6
Fp1-F7
F7-T3
T3-T5
##-##
SpO2
94 94 94 94 94 94 94 94 94 94 93 93 93 93 93 93 93 93 93
Pleth
##-##
A.F.
##-##
##-##
Rib
##-##
##-##
Abd
##-##
ECG1-ECG2
##-##
2 sec.
15:55:45 15:55:47 15:55:49 15:55:51 15:55:53 15:55:55 15:55:57 15:55:59 15:56:01 15:56:03 15:56:05

Figure 10: Case 5, Obscured ECG - Possible Bradycardia Complex Partial Seizure


100 uV
16/06/1994
T4-T6
T3-T5
##-##
ECG1-ECG2
##-##
pleth
##-##
Sp02
99
100
100
99
99
99
99
99
98
97
##-##
##-##
##-##
##-##
##-##
##-##
COMPLEX PARTIAL SEIZURE
WARNING
CLINICAL ONSET
1 sec.
07: 38: 38
07: 38: 39
07: 38: 40
07: 38: 41
07: 38: 42
07: 38: 43
07: 38: 44
07: 38: 45
07: 38: 46
07: 38: 47


100 uV
16/06/1994 LF= 0.5 Hz HF= 10 Hz
File C:\LASER\ch003.P01
T4-T6
T3-T5
##-##
?No QRS Complex
ECG1-ECG2
##-##
pleth
##-##
ECG OBSCURED BY MOVEMENT ARTEFACT
SpO2
97 96 96 95 96 95 96 96 96 97
##-##
##-##
##-##
##-##
##-##
##-##
1 sec.
07:38:50 07:38:51 07:38:52 07:38:53 07:38:54 07:38:55 07:38:56 07:38:57 07:38:58 07:38:59

4.3.5 Tachycardia During Seizures

Increase in heart rate was almost universal occurring in 91% of seizures (39/41). The increase in heart rate was usually early on in the seizure but could precede, coincide with or follow EEG or clinical onset. The increase ranged from 15 to 99 bpm from baseline (mean 40). Maximum heart rates recorded ranged from 78 to 162 (mean 114). Tachycardia also occurred in patients who demonstrated a bradycardia at other times during the seizure. No significant difference was found in terms of maximum heart rate and medication withdrawal for the purpose of recording seizures or maximum heart rate and age.

4.3.6 SpO2 During Seizures

SpO2 readings were difficult to interpret. Small changes in SpO2 were frequently recorded and it was not always possible to exclude movement artefact as a cause of drops in SpO2 as discussed in section 1.3.2.2 (pages 79 - 81).

Extracted SpO2 data from patients during periods with no seizures showed that apparent drops in SpO2 readings occurred when no such drop was expected and were presumed to be artefactual. Small fluctuations were frequent as shown in figure 11. However more frequent fluctuations also occurred in technically less satisfactory recordings. Figure 12 shows frequent loss of signal (straight lines) and apparent desaturations in a fit man during a 13 hour period when no

seizures occurred. Fluctuations were wider during the evening and morning when more movement would have been expected. Figure 13 (case 9) shows 2 episodes of clear desaturation occurring at the time of two complex partial seizures. These seizures were apparently mild to observers but were associated with clear periods of central apnoea.

SpO2 dropped to less than 85% in 10 seizures (6 patients) in association with apnoea. The range was 55-83% (mean 71) and the changes were gradual and consistent with other events recorded and appropriate in timing to the occurrence of apnoea.

As expected SpO2 changes lagged behind changes in respiratory pattern. Mean lag from the onset of the apnoeic spell to the start of a consistent decrease in SpO2 from baseline was 25 s (range 6-49, 6 seizures). Mean lag to the minimum SpO2 recorded was 75 s (range 39 - 108, 7 seizures) and mean lag to the onset of a consistent rise in SpO2 after return of effective ventilation was 23 s (range 11-72, 8 seizures). These figures are only quoted for some of the apnoeic seizures. The reason is that in some seizures quantification is difficult. Patients may for example have inadequate breathing before or after a clear episode of apnoea taking an occasional breath every ten seconds. By definition apnoea would not be present at that time but respiration may be inadequate. However the times quoted above, which are longer for desaturation than resaturation, give an indication of the lag involved. Such delays probably reflect both physiological and technical factors.

Figure 11: Frequent Small fluctuations in SpO2

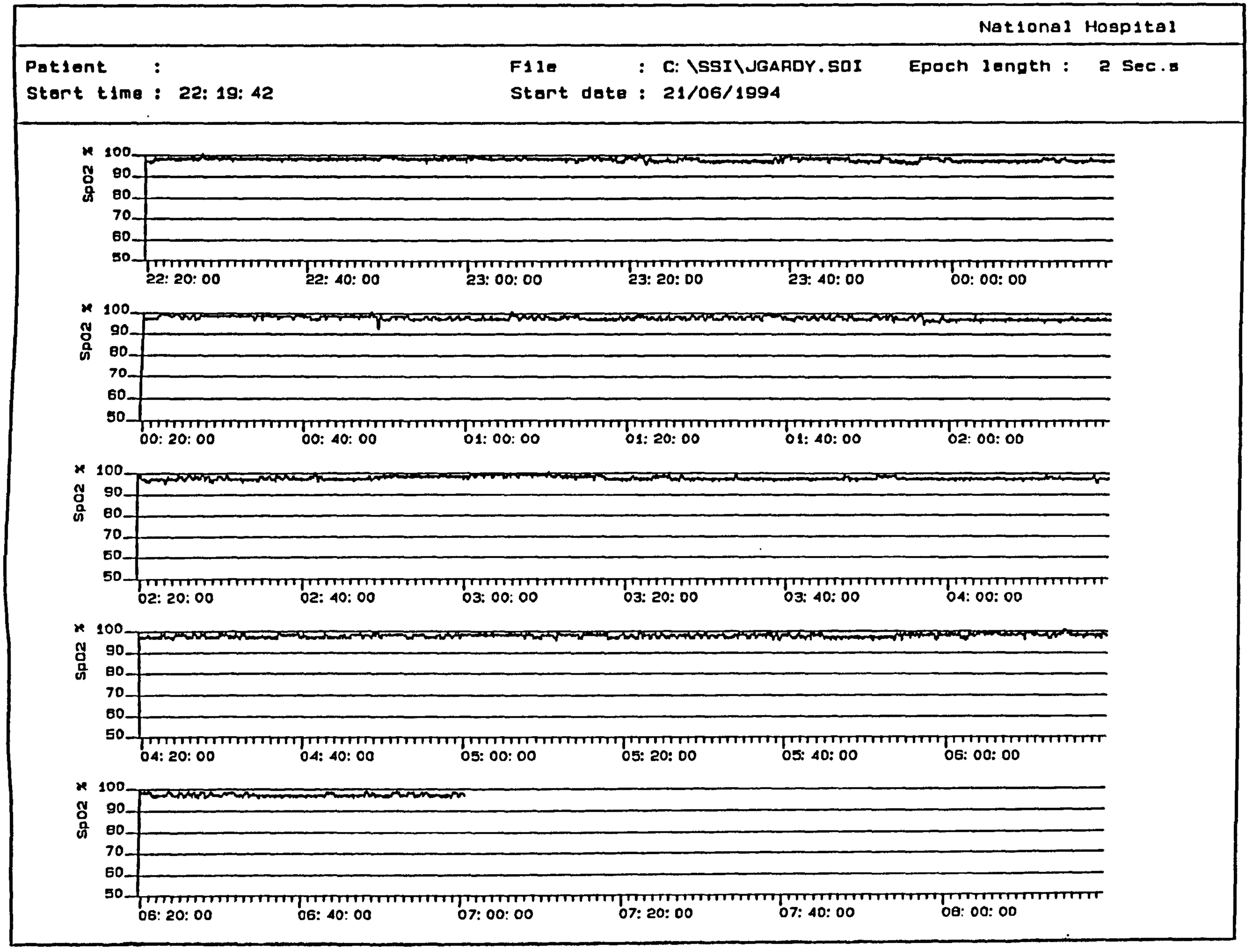


Figure 12: Apparent Desaturation due to Artefact

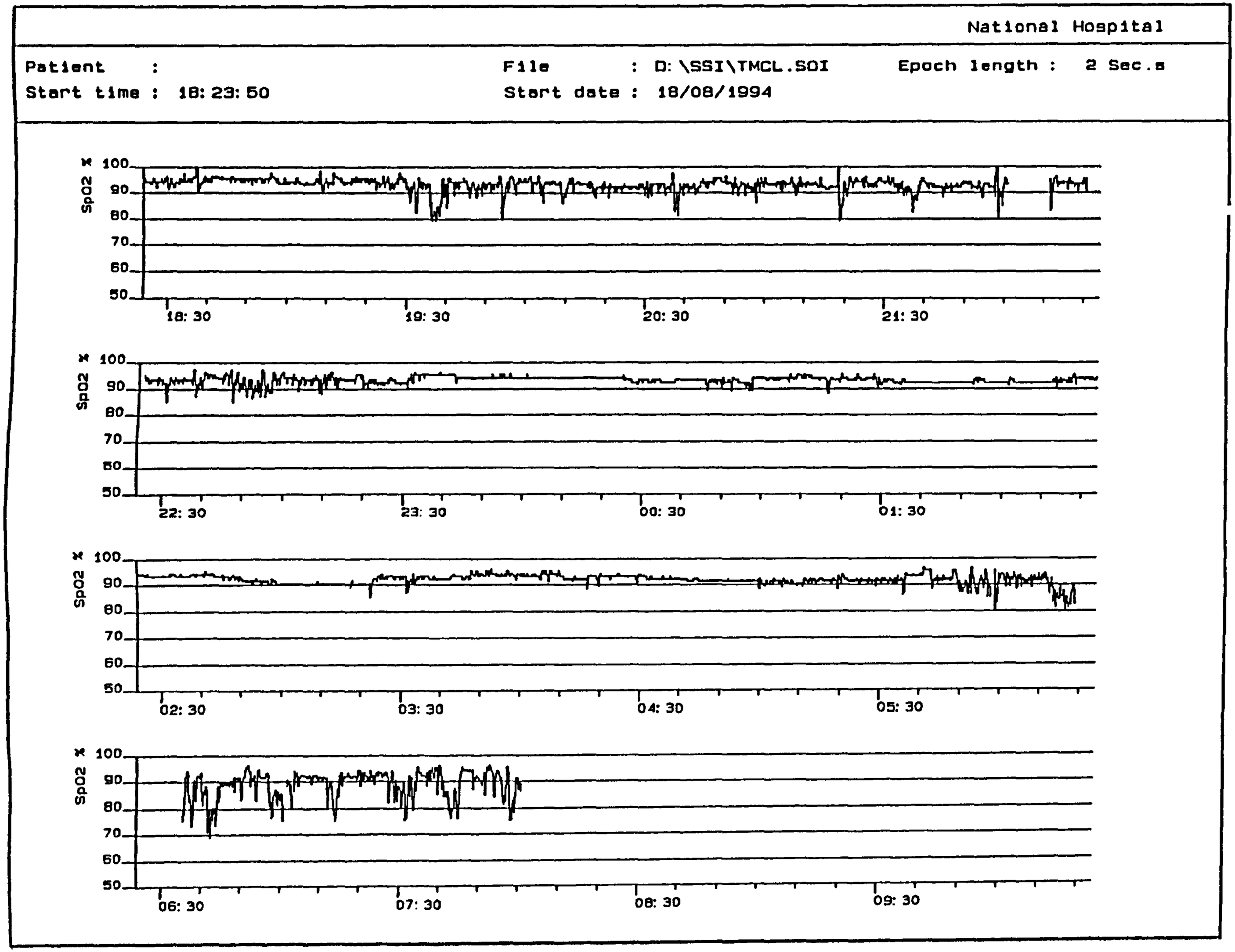
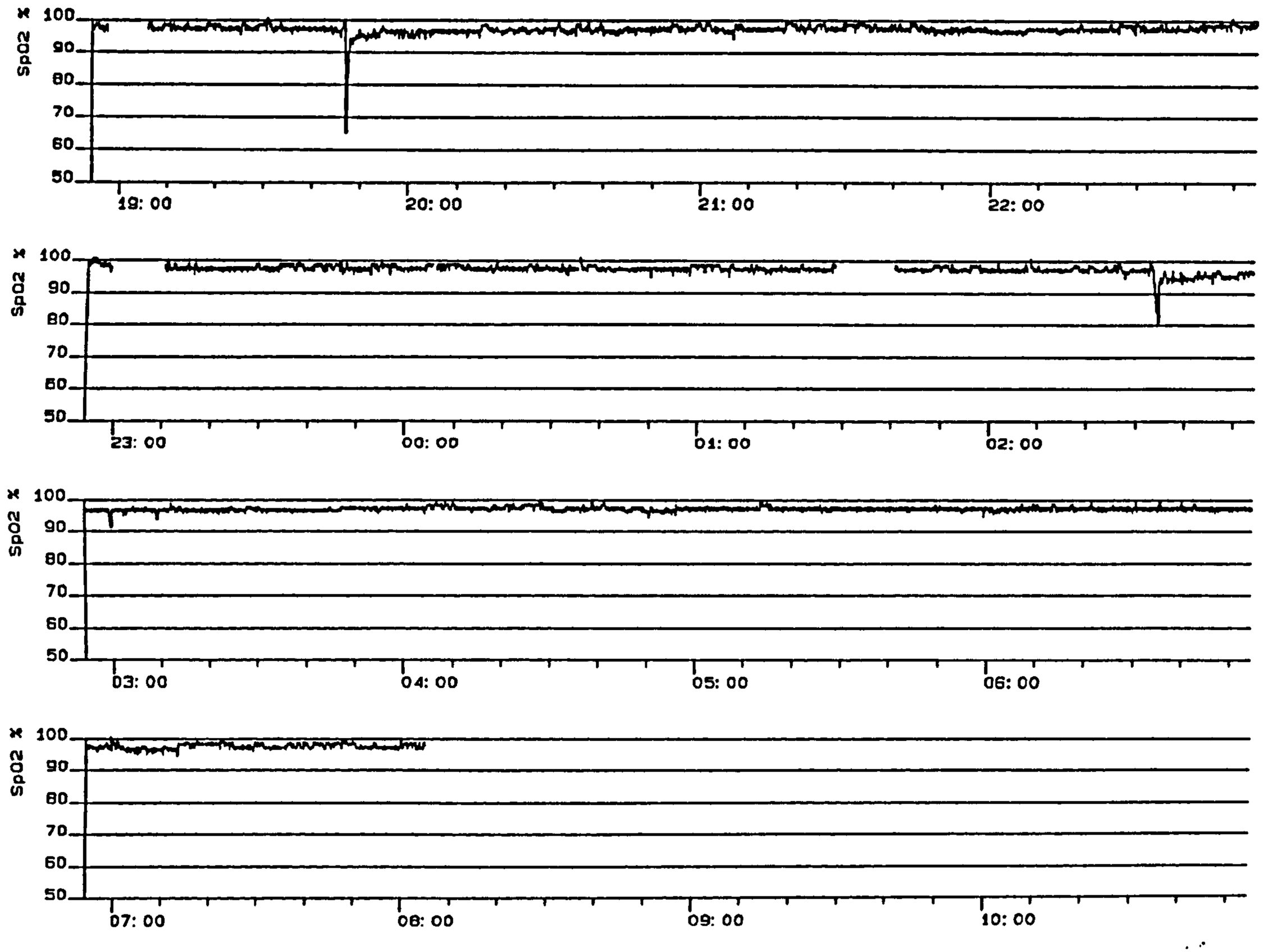


Figure 13: Desaturation in 2 Complex Partial Seizures

National Hospital

Patient :
File : C: \SSI\DCROSS2.SOI Epoch length : 2 Sec.s
Start time : 18: 54: 20
Start date : 13/07/1994



DISCUSSION

5. Discussion

This dissertation comprises of 4 related studies which address the incidence (2 studies), circumstances and mechanisms of sudden unexpected deaths (SUDEP) in chronic epilepsy. A comprehensive review of the literature is also presented.

SUDEP is here defined to include sudden, unexpected, witnessed or unwitnessed, non-traumatic & non-drowning death in epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, where post-mortem examination does not reveal a toxicological or anatomical cause for death.

The aims of this work were as follows:

1. Epidemiology: To establish the incidence of sudden death cases in two selected cohorts with epilepsy; i) an outpatient hospital cohort at a tertiary referral centre, and ii) a cohort of children and young adults with epilepsy and learning difficulty

2. Circumstances: To look at detailed circumstances of sudden death cases by interviewing self-referred close contacts of such cases while substantiating medical details from other sources

3. Mechanisms: To investigate possible mechanisms of sudden death by recording cardiorespiratory parameters during seizures in patients undergoing videotelemetry

4. Risk Factors: To define risk factors and consider methods of prevention by integrating data obtained from the different studies above

5.1 Synopsis of Results

The following is a brief summary of findings. Details are addressed in appropriate sections in the discussion as well as in the results section (4.1 - 4.3; pages 101 - 144).

5.1.1 Epidemiology

Mortality was studied in two selected cohorts. Standardised mortality ratio was 5.1 (95% CI 3.3-7.6) in an outpatient cohort of 601 patients followed up for 3 years (1849 person years) at a tertiary referral centre. The cohort was predominantly one of young adult with 88% between the ages of 15 and 45. SMR was 15.9 (95% CI 10.6-23.0) in the second cohort, a group of young people with epilepsy and learning difficulty (St Elizabeth cohort, 310 persons and 4135 person years). In both cohorts, excess mortality was mainly related to the epilepsy itself rather than to underlying disease. SUDEP incidence of the order of 1:200/year was observed in the outpatient cohort and 1:295/year in the St Elizabeth cohort, and was thus more common than previously thought. Summary findings are outlined in tables 24 and 25.

Table 24: Outpatient Cohort: Summary Results

Number in cohort	601, 330 M, 271 F
Person yrs	1849
Age at entry	Mean 32.5 yrs, range 10 - 80
Total deaths, classification	24, table 8 (page 105)
SMR	5.1 (95% CI 3.3 - 7.6)
Deaths, underlying disease	4 (17%)
Deaths, epilepsy-related	14 (58%)
SUDEP, no	11 (6*F, 5 M)
SUDEP, p.m. performed	10/11
SUDEP, death certificates	Table 10 (page 109)
SUDEP, unwitnessed	8 (3 incomplete information)
SUDEP, intractable	10/11
SUDEP, history of TCS	11/11
SUDEP, race	1 Asian, remainder Caucasian
SUDEP, age at death	Mean 28.6 yrs, range 18 - 34
SUDEP, relation to age	Table 9 (page 107)
SUDEP, yrs of epilepsy	Mean 20.8 yrs, range 14 - 30
SUDEP, AED	Mean 2.36, range 1-4
SUDEP, Epilepsy syndrome	see page 107
SUDEP, IQ	5/11 IQ < 80+

* 2 with additional factors, see text page 106

+ only one with severe mental handicap

Table 25: St Elizabeth Cohort: Summary Results

Number in cohort	310
Sex	103 M, 207 F
Person yrs, F, M, ratio	4135 yrs, 2984, 1151, 2.6:1
Age range, person yrs	Table 15 (page 117)
Total deaths, classification	28, table 13 (page 113)
SMR	15.9 (95% CI 10.6-23.0)
Deaths, underlying disease	4 (14%)
Deaths, epilepsy-related	20 (71%)
SUDEP, no	14 (10 F, 4 M)
SUDEP, p.m. performed	11/12, 2 unknown (pages 114-116)
SUDEP, death certificates	Table 14 (page 116)
SUDEP, circumstances	Table 14 (page 116)
SUDEP, unwitnessed	10/12 (2 no information available)
SUDEP, history of TCS	14/14
SUDEP, age at death	Mean 19 yrs, range 10-28
SUDEP, relation to age-group	Table 15 (page 117)
SUDEP, yrs of epilepsy	Mean 17 yrs, range 8 - 26
SUDEP, IQ	1/14 "globally retarded" 13/14 mean IQ 65 (range 40-98)

5.1.2 First-Hand Evidence of Circumstances of Sudden Death

In a separate study, 27 interviews of self-referred bereaved relatives of cases of sudden unexpected deaths were conducted. Twenty cases (10 male, 10 female) fulfilled the definition of SUDEP. Mean age was 27 years, range 14 - 51, with 19 aged between 14 and 36. Nineteen of the deaths were unwitnessed with circumstantial evidence suggestive of a seizure found in the majority (table 21, page 126). In at least 6 cases the position in which the body was found was such that suffocation may have been a contributory factor with 3 found face down into the pillow. Eight patients were classified as having primary generalised epilepsy (table 18, page 123).

Most relatives had previously understood that epilepsy could not be fatal and experienced difficulty in coming to terms with their unexplained loss.

5.1.3 Possible Mechanisms of Sudden Death: Cardiorespiratory Changes During Telemetry

A study of ictal cardiorespiratory changes was performed in an EEG/video telemetry department. Apnoea was recorded in 10/17 patients or 20/47 clinical seizures (3 secondary generalised, 16 complex partial and 1 tonic). The apnoea was mainly central although obstructive apnoea was also recorded. An increase in heart rate was commonly observed occurring in 91% of seizures. Bradycardia/sinus arrest occurred in at least 4 patients (mean

RR interval 5.36s, range 2.8-8.6) within the context of a change in respiratory pattern. In 3 cases this occurred during an apnoeic spell and in the fourth during repeated prolonged forced expirations interrupted by brief inspirations. SpO2 dropped to less than 85% in 10 seizures (6 patients). It is speculated that such mechanisms are likely to underline most cases of SUDEP (see section 5.4.3, pages 169 - 173).

5.2 Problems of Definition

The definition of sudden death in epilepsy remains controversial. The use of terminology in this field has varied between studies and indeed no consensus has been reached. Writers at the turn of the century (section 1.1.8.2, pages 47 - 55) used the term sudden death in a broad sense that embraced accidental fatalities as well as other seizure-related deaths, including those with coexistent contributory cardiorespiratory pathology. Current use of the term is much more restrictive.

The acronym SUDEP is used in this dissertation to refer to sudden *unexpected* death in epilepsy as defined above (page 145). Alternative acronyms include sudden *unexplained* death in epilepsy (SUD, SUDEP) and sudden *unexplained* and *unexpected* death in epilepsy (SUUDEP). Problems of definition revolve around the use and implications of the word unexplained. Some authorities, for example have taken this to imply exclusion of known seizure deaths, and indeed some studies list sudden

unexpected deaths and seizure-deaths separately without necessarily clarifying whether the latter were witnessed seizure-related deaths, or whether seizures were presumed on the basis of circumstantial or other evidence (Jallon et al 1989, Iivanainen & Lehtinen 1979, Klenerman 1993). However, in addressing sudden death in epilepsy, one soon perceives difficulties in unequivocally classifying individual cases into one or other category, similar to those encountered in establishing if an unwitnessed fatal accident or drowning in a patient with epilepsy was consequent to a seizure. Such difficulties relate to the availability and interpretation of largely circumstantial evidence pertaining to what is often an unwitnessed event. The definition used in this work therefore does not make this distinction, thus acknowledging that evidence in favour of a seizure may be absent, consistent with or, indeed, highly suggestive of a seizure. While the presence of such evidence may not be absolute, its absence similarly does not exclude a seizure.

Confusion also arises in the interpretation of the term unexplained as applied to likely or possible mechanisms. If a sudden death occurs in a patient with chronic epilepsy, even within the context of a witnessed habitual seizure, and post mortem examination shows evidence of severe ischaemic heart disease, such a death is appropriately not classified as a case of SUDEP. How, however, should cases of clear aspiration or obstruction with a food bolus be classified? The definition used in this work excludes such cases, although they are

seizure-related deaths without coexistent unrelated pathology. The situation becomes more difficult in the presence of evidence that may be considered suggestive of postural asphyxia. This may be based on the history of the position in which the body was found (which is often incomplete) or on post-mortem findings. Regarding the latter, forensic pathologists have questioned whether asphyxia has unequivocal post-mortem signs (Gordon 1955, Zaini & Knight 1982, Leadbeatter & Knight 1988, Rao & Welti 1988). Although initially described as pathognomonic of mechanical interference with respiration, the significance of subpleural, subpericardial and subendothelial haemorrhages has been disputed particularly that they may also develop spontaneously after death (Gordon 1955). As for subconjunctival petechiae, which occur in mechanical asphyxia, these also occur in other conditions, in particular cardiovascular disease. Rao & Welti (1988) retrospectively reviewed 5,000 results of autopsies and found that conjunctival haemorrhages were mentioned in 227 instances (4.5%). Of those, 65 had died of cardiovascular disease and 76 were asphyxial deaths. Their conclusion was that *"conjunctival petechiae were most often the result of hypoxia coupled with an acute increase in vascular cephalic pressure. The latter factor may be the consequence of mechanical vascular obstruction or acute right heart failure."* Raised cephalic venous pressure and hypoxia may occur in seizures independently of extrinsic mechanisms. Furthermore, petechial haemorrhages may be found at post-mortem following resuscitation (Leadbeatter & Knight 1988).

Thus, cases of possible postural asphyxia are included within the definition used in this study, as are cases with post mortem findings of mucoid secretions in the airways or varying degrees of pulmonary oedema, a very common finding. The possible contribution to death of suffocation *"during post-epileptic insensibility"* (Gowers 1885) and pulmonary oedema (Terrence et al 1981) in such cases is not excluded, but their exact role in what might be a multifactorial event is difficult to define with certainty in individual cases.

Another subgroup of patients where there is no uniform agreement regarding inclusion in the SUDEP category is that of individuals found dead in the bath. The presence of clear evidence of drowning on post-mortem excludes such cases. Difficulty arises, however, if no such evidence is found, given that, even in definite drowning cases, evidence may be lacking (Greene 1965). In this study the approach adopted was that a case would be included if there was no evidence of immersion, and excluded if the head was found to be partly or wholly submerged under water. Two such cases were excluded in the interview study.

There is clearly a need for a consensus in the literature and among researchers in the field regarding definitions and classification of epilepsy-related deaths. Any classification must take into account not only theoretical grounds, for example the need to differentiate where possible between extrinsic or intrinsic mechanisms, but also the information

usually available in such cases. A classification needs to be workable, its merit the extent to which it is applicable. A consensus might perhaps be best achieved under the auspices of the International League Against Epilepsy, and I will suggest that this is considered by the ILAE commission on classification.

The forthcoming discussion addresses limitations of the present work and integrates the findings with results from previous studies. The following areas will be covered:

* SUDEP incidence and overall mortality in chronic epilepsy (5.3)
* Evidence in favour of seizures in SUDEP, and modes/mechanisms of seizure-related deaths (5.4)
* Risk factors in SUDEP (5.5)
* The unwitnessed nature of many SUDEP deaths (5.6)
* Perceived needs of bereaved relatives (5.7)
* Potential for prevention of seizure-related deaths (5.8)
* Future research (5.9)

5.3 SUDEP Incidence & Overall Mortality in Chronic Epilepsy

One area of uncertainty in this field is the magnitude of the problem. Results of different studies may appear at first contradictory, and as in epidemiological studies in epilepsy generally, issues relating to selection bias often add to difficulties in interpretation. Yet a critical analysis of incidence data from different sources accounting for difference in patient selection shows a broadly consistent picture (section 5.3.2, pages 157 - 161). Rodin pointed out in his textbook on prognosis (1968) that *'general statements covering all epileptics are likely to be an oversimplification'*. Results from one cohort cannot be extrapolated to another, yet are valid in their context and have implications to clinical management.

5.3.1 Excess Overall Mortality, Epilepsy Deaths & Clinical Implications

As expected the result of the two epidemiological studies presented confirm that mortality in chronic epilepsy is increased compared to the general population. In the outpatient cohort SMR was 5.1 (95% CI 3.3-7.6), and in the St Elizabeth cohort SMR was an even higher 15.9 (95% CI 10.6-23.0). The higher rate in the St Elizabeth cohort reflects the sex breakdown in the sample and the very low mortality in the general population in young females. The increase is in agreement with published data, however there are particular

features of these cohorts that should be noted.

Both cohorts largely represent groups with long-standing chronic epilepsy and are clearly not representative of population based cohorts; while the latter are essential to the true understanding of the epidemiology of epilepsy, observations from population-based studies cannot be extrapolated to chronic epilepsy. In population-based studies, there is an initial excess mortality due to underlying or associated disease and remission rates are high (Cockerell et al 1994a, Hauser et al 1980, Sander et al 1990). Patients with chronic epilepsy on the other hand constitute a subgroup with a different outlook: that of low remission rates and increased mortality primarily as a direct consequence of the epilepsy. The latter has been clearly shown in the two cohorts studied. In the outpatient cohort, in only 4 cases (17%) was death due to underlying disease of which epilepsy was a symptom, and at least 14 deaths (58%) were considered epilepsy related (table 8 - page 105). Similarly, in the St Elizabeth cohort 20/28 deaths (71%) were considered epilepsy related, with only 4 deaths related to underlying disease (table 13 - page 113). The excess mortality was particularly marked in young patients with chronic epilepsy.

There are clear implications to clinical management. Decisions in intractable cases relating to treatment options whether medical or surgical can only be made with reference to underlying morbidity and mortality from the condition itself.

Patients with chronic epilepsy contemplating surgery for example need to consider a number of factors including risks of presurgical evaluation (whether related to controlled drug withdrawal or depth electrodes if indicated), peroperative risk, likelihood of improvement as well as the risks inherent in uncontrolled disease. At present it is unlikely that this information is presented in full to patients, in particular where it concerns the risk of death due to the epilepsy. Similarly, the background risk of the condition itself is not usually addressed when potential side-effects relating to antiepileptic drugs, whether established or experimental, are discussed, or how aggressive the approach to drug therapy should be.

My study in this area has changed practice. The background risk demonstrated in the outpatient cohort is now taken into account in management decisions by physicians working at the National Hospital where the study was performed. It has also become our policy to give patients the opportunity to discuss this issue, where appropriate.

5.3.2 Incidence Data

In the era prior to modern antiepileptic therapy, Spratling stated that a non-accidental death from seizures occurred in 3-4% of patients with epilepsy (1904). Leestma, whose prospective study (1989) was based on coroner's cases in Cook

County, Illinois estimated an incidence of between 1:370 and 1:1,110/ year and probably higher in those aged 20-40.

Jick et al (1992), in a recent population study based on antiepileptic drug prescribing in the age-group 15-49 found an incidence of approximately 1:1000 years at risk (0.9-1.3:1000 years at risk). Drowning, however, could not be ruled out in 3/11 reported cases, which would tend to overestimate the risk. On the other hand cases with acquired epilepsy were excluded. Such cases are potentially more severe, and their exclusion may thus underestimate risk.

On current evidence a population based incidence of 1:1000 per year for all patients with epilepsy is likely to be close to the true incidence. However, this cannot be extrapolated to selected groups.

At one end of the spectrum, only 2 sudden death cases were observed in the Medical Research Council Antiepileptic Drug Withdrawal Study with over 5000 patient years, both deaths having occurred in patients randomised to continue medication. In this study, a condition for entry was a seizure-free period of at least 2 years on AED. This suggests that controlled patients whether as a result of treatment or whether as a result of inherently less severe disease (as judged by seizure control) have an extremely low risk of sudden death.

Similarly in the National General Practice Study of Epilepsy

(NGPSE, Cockerell et al 1994a) no sudden death cases were reported in 3712 person years relating to 564 definite cases. Although this is a community based study, it would be inappropriate to expect a 1:1,000 a year incidence of sudden death (or 3-4 cases). This figure is based on studies of prevalent cases in the community. The cases ascertained by the NGPSE are incident or newly diagnosed cases including single seizures. Overall three year remission rates were around 60% after five years of follow-up with remission rates rising with continued follow-up and only 60% or so of patients on treatment (Cockerell 1994b). Thus, only some of the cases making up this cohort contribute to the pool of chronic cases. The finding of no cases of sudden deaths is therefore not as surprising as may first appear.

At the other end of the spectrum, in a series of adult patients enrolled in an epilepsy surgery programme (Dashieff 1991) in Pittsburgh, 7:150 patients died a sudden death during some 5 years of follow-up, a rate closer to 1:100/year. Although the cases described were not altogether typical, this rate reflects a considerably higher incidence in an intractable group of patients enrolled in a surgery programme.

The rate of such deaths in the recent mortality study from the Chalfont Centre for Epilepsy, a long-term residential centre for people with severe epilepsy and often learning difficulty, was 1:260 per year (Klenerman et al 1993) if one combines seizure-related and other unwitnessed deaths (excluding

documented status epilepticus). Although sheltered, most residents at Chalfont have their own rooms and are not under 24-hour supervision.

In the first of the two cohorts studied in this work, the outpatient cohort at a tertiary centre, the overall incidence of sudden death was of the order of 1:200/year. An even higher incidence is obtained if those aged between 15 and 35 are considered separately (table 9, page 106). This cohort is typical of patients attending a tertiary referral centre with the majority of patients being young adults with chronic epilepsy. In the second cohort, St Elizabeth's cohort, the incidence was 1:295/ year. The latter is a younger cohort of individuals with chronic epilepsy and variable learning difficulty. In both cohorts the epilepsy is often severe.

In conclusion, epidemiological studies all support the view that cohorts with less well controlled epilepsy carry a higher risk of sudden death. It is not possible to entirely refute the argument that the risk reflects underlying pathology which also manifests as poor seizure control rather than the risk being defined by poor seizure control per se. This seems unlikely given the generally static nature of underlying pathology in chronic epilepsy. If uncontrolled epilepsy carries a higher risk of death, then improved control, by whatever means, should lower that risk, with the proviso that treatment itself, whether surgical or medical, does not carry a greater risk, not only of such life-threatening complications as liver failure

or aplastic anaemia, but also of cardiac arrhythmias.

A controlled mortality study in chronic epilepsy of treatment vs no treatment would be unethical. Mortality data from untreated populations may be of interest in this regard although there are likely to be many confounding variables.

An estimate based on 250,000 patients with epilepsy in England and Wales (75,000 uncontrolled), and a yearly sudden death incidence of 1:1000/year in a general epilepsy population (1:300/year if uncontrolled) suggests that some 250 patients with epilepsy per year may die unexpectedly. This figure excludes deaths from status epilepticus, traumatic/drowning seizure-related deaths as well as seizure-related deaths with co-existing unrelated cardiorespiratory pathology.

Although any seizure may constitute a risk to life, and every attempt must be made to prevent seizures, it is in cohorts with uncontrolled epilepsy that the risk is substantial enough to be taken into serious consideration when potentially hazardous management decisions are decided upon (see section 5.3.1, pages 155 - 157).

5.3.3 Death Certification

The lack of consistency in death certification in such cases has meant only limited information can be obtained from

national mortality data. Causes of death as certified in SUDEP cases vary (tables 10, 14, 20; pages 109, 116, 125) with mechanisms often assumed rather than observed. Status epilepticus in particular is often recorded on the death certificate even when unsubstantiated. In some cases, an open verdict is recorded, with the consequence that the death does not feature in epilepsy mortality statistics at all. However, this was the case in only 2/44 death certificates. Conversely in only one death certificate was epilepsy recorded as the cause of death where unascertained in my view would have been more appropriate (see exclusions - interview study, section 4.2.1, pages 119 - 120).

Where there is suggestive evidence for a seizure and no evidence of trauma, I would suggest that 'Epileptic seizure/Known epilepsy' could be recorded as the cause of death, and where such evidence is inconclusive or absent then 'Sudden death/ Known epilepsy' may be used. The latter category may still be seizure-related. In both situations it would be useful to state whether the terminal event was witnessed.

Another issue is that unexpected deaths in patients with epilepsy may be automatically attributed to seizures without appropriate assessment; this does not appear to be the case in the U.K. at present (although toxicology is not routinely performed), but may be a risk as the phenomenon becomes more widely known. Guidelines for coroners for the assessment, documentation and certification of such cases are required.

5.4 Evidence in Favour of Seizures in SUDEP, & Modes/Mechanisms of Seizure-Related Deaths

5.4.1 Evidence for a Seizure in SUDEP Cases

Leestma et al (1989) in the Cook County study, the largest recent series of 60 such deaths reported evidence for a seizure in about half the cases. Details of what constituted admissible evidence was not outlined. Most epidemiological studies do not address this in detail (Schwender & Troncoso (1986), Harvey et al (1993), Lip & Brodie (1992). This is to be expected as detailed information in this regard is not easy to obtain nor may it be the aim to do so in incidence studies. Terrence et al (1975) in a study of 37 cases, states that 9 patients died "*as a result of a single seizure or a few seizures in the presence of witnesses*" but does not report on evidence in favour of seizures in unwitnessed cases. Jallon et al (1989) reports 58 deaths of definite or possible seizures as compared to 37 unexplained cases. The definite cases were classified as such on the basis of "*physical signs of seizure*" (not listed) and the possible cases (23) were classified as such on the basis of "*death place, body position, death circumstances*" (not defined). Earnest et al (1992) reported on the percentage of cases with tongue biting which was present in "*half of 18 in which the tongue was examined*" but did not comment on other features. Hirsch & Martin (1971) reported on 19 cases, 8 of whom were witnessed. Of those four had TCS and 2 possible tonic seizures. Again evidence in favour of a seizure in the

unwitnessed group was not addressed.

It is clear from this account that detailed circumstances are lacking in many epidemiological studies. Similarly, the main purpose of the two cohort studies in this work was to look at incidence. The main aim in the interview study, however, was to look at circumstances to see what light this could throw on the mechanisms of sudden death.

There are many limitations to the interview study, particularly with regard to assessment of risk factors where it is not possible to draw conclusions beyond those of an uncontrolled descriptive nature. However, this aspect of the work where detailed histories were obtained, was most useful in addressing two important questions relating to position in which the body was found and evidence in favour of a seizure at the time of death.

Although more detailed information was obtained per case than is usually available, the study was retrospective. As data was not compiled at the time of death, information obtained may have been incomplete. However, every effort was made to corroborate available data through other sources. The results suggest that the proportion with evidence for a seizure is even higher than previously reported. Such evidence was found in 17/20 SUDEP cases. It has to be stressed that evidence in an unwitnessed case is often circumstantial. Such evidence may include any of the following: a bitten tongue or lip,

incontinence, partial or complete fall off the bed, blood or pink secretions on bedding, a disrupted environment, noise heard suggestive of a seizure, facial expression as in a seizure, or death occurring in the context and/or timing of habitual seizures (table 21 - page 126). More than one of these features may be found in an individual case.

These circumstantial findings support the view that the majority of SUDEP cases are seizure deaths and that the distinction some authors have drawn between those that occur within the context of a witnessed single seizure death, and between sudden unexpected unwitnessed deaths in patients with epilepsy may not be valid in most cases.

It must be emphasized that the view that the majority of SUDEP cases are seizure-related does not preclude the possibility that a non-ictal primary or secondary cardiac arrhythmia (for example due to AED treatment) may occur in a patient with epilepsy. Nor does it preclude the possibility that patients with a potentially fatal primary cardiac disorder presenting with blackouts may be misdiagnosed as epilepsy. This is not the subject of this dissertation but is an important area in its own right (Jallon 1991, Stephenson 1990). In the outpatient cohort and in the interview study detailed medical documentation was usually obtained and cases excluded if the diagnosis of epilepsy was not supported. Such details were lacking for the St Elizabeth cohort but given the medical and specialist back-up available to the school, misdiagnosed cases

are unlikely. In the outpatient cohort ECG was available for only 3 cases. In these, QT interval corrected for heart rate was normal as has been reported by Tavernor et al (1994) in similar cases.

5.4.2 Modes of Death from Seizures

As already mentioned, it is worth emphasizing that the relatively strict definition of SUDEP used in this study does not include all sudden unexpected deaths in a seizure even in the absence of coexisting cardiorespiratory pathology. The interview study was particularly useful in outlining different modes of death in seizures although, in view of potential bias inherent in self-referral, conclusions regarding the relative importance of different causes cannot be drawn.

As has already been stated, in addition to deaths from surgical or medical treatment or from suicide (which may be epilepsy related), deaths in epilepsy may be a direct consequence of seizures by a variety of different mechanisms. These may be usefully summarised at this stage (table 26). Accidental traumatic or drowning deaths consequent to a seizure and witnessed status epilepticus are self-evident causes, although as previously noted (section 1.1.7, page 31) the latter may often be more appropriately classified as due to underlying disease.

Patients may die in a seizure due to intrinsic presumed

cardiorespiratory mechanisms. Apnoea, pulmonary oedema, bronchial secretions, hypoxia and sinus arrest are all known to occur in seizures and are not mutually exclusive (section 1.2, pages 56 - 74). In some, extrinsic mechanisms may contribute, with the position in which the body is found and post-mortem findings of pressure markings and petechial haemorrhages suggesting suffocation in an unconscious individual. This was felt to be the case in at least 6/20 cases in the interview study, including 3 cases found face down into the pillow. Although the presence of petechial haemorrhages is not specific as discussed above (page 152), they were significantly more likely to be mentioned in the post-mortem report in cases with a history compatible with suffocation as a contributory factor. Petechial haemorrhages are also known to be more likely to occur where resuscitation has been attempted (Leadbeatter & Knight 1988) although this was not the explanation in this study. It is of interest that in only two cases did the relatives interviewed spontaneously comment on the distorted facial expression found 'as in a seizure', perhaps suggesting that most deaths did not occur instantaneously at the height of a seizure.

Whereas SUDEP cases have been the subject of renewed interest, other modes/causes of death form seizures have tended to be overlooked. While not falling within the strict definition of SUDEP, in that post-mortem findings reveal a cause for death, vomiting with aspiration or airway obstruction by food for example may also occur in a seizure.

Finally, death in a seizure may be more likely in the setting of additional unrelated pathology such as ischaemic heart disease. Patients with both ischaemic heart disease and chronic epilepsy for example may be at particular risk of seizure-related deaths. Death certificates, as in one of two such cases described in the interview study, may not refer to the known diagnosis of epilepsy despite a habitual witnessed seizure at the time of death. It is not possible to estimate the numbers involved, however, in a study reported by Annegers et al (1984), based on mortality findings in an unselected population with epilepsy, an excess of ischaemic heart disease in persons under 65 was found.

Table 26: Deaths due to Seizures

- Status epilepticus

- Traumatic or drowning deaths consequent to a seizure

- SUDEP (majority seizure-related)
    * Intrinsic presumed cardiorespiratory mechanism e.g.
        Apnoea (obstructive or central)
        pulmonary oedema
        bronchial secretions
        hypoxia
        sinus arrest (? Other Arrhythmia)
    * Possible extrinsic contributory mechanisms e.g.
        suffocation

- Seizure-related deaths with a clear mechanism on p.m. without co-existing unrelated pathology
    e.g. vomiting with aspiration
        airway obstruction by food

- Seizure-related deaths due to co-existent pathology e.g.
        ischaemic heart disease

5.4.3 Mechanisms of Sudden Death

Theories put forward for the mechanism of sudden death in epilepsy have concentrated on autonomic instability during or soon after overt or subclinical seizures and have included the possible role of cardiac arrhythmias as the main event leading to sudden death in epilepsy. Yet, despite occasional case reports, systematic studies have generally failed to support the hypothesis that malignant cardiac brady/tachyarrhythmias commonly occur during seizures (section 1.2.2, pages 66 - 70). Recent studies have focused on heart rate changes in isolation, although hypoxia secondary to central or obstructive apnoea or pulmonary oedema are alternative mechanisms. Both cardiac and respiratory disturbances or other as yet unknown mechanisms may play a part. In this study of seizure-recordings, respiratory parameters were also included demonstrating that it is possible to record respiration non-invasively during seizures, and that apnoea and bradycardia do occur, with heart rate changes related to respiration. In spite of the fact that most seizures recorded were complex partial, cardiorespiratory changes were often marked.

Apnoea was recorded in 10/17 cases and bradyarrhythmias in at least 4/17. The number with bradycardia may have been higher as the ECG tracing during seizures was sometimes obscured by movement artefact. Bradycardia/sinus arrest occurred within the context of a change in respiratory pattern. As outlined in section 1.2.1.3 (pages 64 - 65), apnoea is known to be a time

of increased risk of bradycardia and sinus arrest with heightened sensitivity of vagal motoneurones, a state potentiated by hypoxia. Direct parasympathetic stimulation as part of the seizure discharge may play a part, but is unlikely alone to account for the changes. Although overactivity of both sympathetic and parasympathetic systems is known to occur in seizures, (benign) tachycardias are usually predominant as indeed was the case in this study. It is of interest that in 3/4 cases brady-arrhythmias were not observed at or soon after the onset of the seizure occurring later during an apnoeic spell supporting the view that bradycardia is primarily potentiated by cardiorespiratory reflexes. This view is in keeping with the observation that SUDEP deaths are more common in young patients, given that the magnitude of cardiorespiratory reflexes diminishes with age (section 1.2.1.3, page 65). A marked decrease in SpO_2 without accession the bradyarrhythmias to occur but would be an additional contributory factor.

The results outlined clearly show that interpretation of cardiac changes in particular bradyarrhythmias is incomplete without recording respiratory parameters at the same time. Tachycardias on the other hand were very frequent as previously reported. This is considered a sympathetically mediated direct consequence of the seizure discharge. Apnoea is known to occur in generalised seizures, and in this study has also been shown to occur not infrequently in partial seizures and was observed in 20/47 seizures recorded in 10 of 17 patients (section 4.3.3,

pages 132 - 133).

Whether patients consistently shown to have cardiorespiratory changes during seizures are more at risk of sudden death remains speculative.

The relationship between blood gas concentrations and termination of apnoea during seizures would be of particular interest but at present would require more invasive measurements that those undertaken in this study. Under normal conditions it is hypercapnoeic, rather than hypoxic, ventilatory drive that is predominant. Although CO2 can be measured transcutaneously, this involves skin heating and necessitates moving the device at regular intervals. This, coupled with long response times, limit applicability to seizure recordings at the present time. It would also be informative to be able to record blood pressure changes continuously during seizures however non-invasive available methods at present are not well-suited for such a purpose, principally because of movement artefact.

5.4.4 Technical Issues

On the whole, patients tolerated the extra recordings well. The airflow sensor was, probably owing to its position, the least popular. The other intermittent disturbance related to the oximeter alarm.

In only one patient was the recording such that the study was uninformative. However, individual parameters were not always informative in all patients at all times, as shown in the included examples (figures 6-10). It must be stressed that interpretation relied on integrating data from more than one source, including video and sound recordings, while taking into account the patient's activity during the seizure. Reference has already been made to the potential for bradycardia to be obscured by artefact. Similarly SpO2 data cannot be interpreted in isolation. Airflow and respiratory effort data are only semi-quantitative. Nevertheless, the additional information obtained was such that consideration is being given to the routine inclusion of these additional parameters during EEG/Videotelemetry in selected patients in the department where this study was performed. A longer term study is likely to provide additional information of changes in different seizure-types including post-ictal changes in generalised seizures.

5.4.5 Summary

In summary, where detailed information in sudden death cases is obtained, circumstantial evidence suggests that the majority of such deaths are seizure-related. Cardiorespiratory reflexes may facilitate the occurrence of potentially fatal bradycardia/sinus arrest during ictal apnoea and hypoxia. In my view, such mechanisms are likely to underline many cases of SUDEP.

5.5 Risk Factors in SUDEP Cases

Before discussing relevant findings in this study, risk factors for sudden death in epilepsy reported in the literature may be usefully reviewed (section 1.1.8.1, pages 41 - 46). Young adults are considered at higher risk and the mean age of sudden death is usually in the early thirties although the range covers all age-groups. Leestma et al (1989) reports that male Afro-Americans, with a history of excess alcohol intake, who are noncompliant and who have had epilepsy for less than ten years are particularly at risk. How important these factors are in different settings is unclear. Leestma also reported a high male:female ratio of 3.3:1. Other studies have shown a smaller difference (Lip & Brodie 1992 M:F ratio = 1.4:1, Earnest et al 1992 1.75:1, Hirsch & Martin 1971 1.7:1, Terrence et al 1975 1.5:1). The relation to seizure control is not clear with control at the time of death not necessarily poor (Brown 1992). Patients in the vast majority have a history of generalised tonic clonic seizures. Studies also report a higher risk in patients with remote symptomatic epilepsy and in association with mental handicap.

5.5.1 Age

Although sudden deaths do occur in older and younger age groups those at highest risk fall between the ages of 15 and 35.

In the outpatient cohort as a whole older patients were not

well represented with 88% of all 601 patients between the ages of 15 and 45 (figure 5, page 102). Reasons for this are not entirely clear. Possible explanations include remission, referral and discharge patterns, amelioration of epilepsy with age or cumulative mortality. Remission is likely to be of minor importance in such a group with predominantly chronic epilepsy with a mean duration of epilepsy of 19 years, with 10% only having epilepsy of less than 5 years duration and 24% less than 10. Sander (1993) has recently reviewed published remission rates in different cohorts. Although "*as many as 70-80% of people developing seizures for the first time will eventually achieve terminal remission*", most remissions occur early after diagnosis. The potential contribution of cumulative mortality may be further assessed by a longer term study of the same cohort which is planned. Whatever the reason for the age-distribution, this needs to be born in mind in interpreting results.

The observed cases of sudden death were all within the age-range 15-34, where the incidence was about 1:100 (Table 9, page 107). With an overall observed incidence of 1:200/year, 3-4 such deaths would have been expected among those in other age-groups but none were observed. Although the numbers are small, the incidence among young adults cannot be extrapolated to older age-groups nor cumulative mortality calculated on the basis of this data. It may well be that the risk peaks in young adults then declines. The alternative explanation that those at risk die early in the course of their illness seems unlikely

as patients in these studies had a long standing history of epilepsy. Table 12 (page 112) shows sudden death cases in relation to person years in the St Elizabeth cohort. The trend is also towards higher rates in young adults although the numbers are small.

If, as seems likely on current evidence, in the setting of continuing chronic epilepsy and in the absence of primary cardiorespiratory pathology, the risk of sudden death peaks in early adulthood, both physiological parameters and social parameters need to be considered. Physiological parameters may relate to seizure characteristics and/or autonomic function. The expression of epilepsy is age-related with transition from childhood to adolescence/adulthood one of the landmarks. Furthermore, cardiorespiratory reflexes are more pronounced in youth. Social parameters relate to the transition from the supervised home environment to relative independence. It is likely that both physiological and social factors influence the higher incidence observed in young adults.

5.5.2 Sex

Both males and females were equally represented in this study. In the outpatient cohort there were 5 male sudden deaths and 6 female (in 2 with additional factors - see section 4.1.1.4, page 106), representing a 0.83:1 male:female ratio (male:female ratio in the whole cohort 1.22:1). In St Elizabeth cohort there were 4 male sudden deaths and 10 female,

representing a 0.4:1 male:female ratio (male:female ratio in the whole cohort in relation to person years 0.39:1). Ten male and 10 female cases were the subject of the interview study.

While the literature highlights non-compliant young men with a heavy alcohol intake as particularly at risk, such patients are not necessarily representative of SUDEP cases in general. These characteristics may be considered some of many factors that influence seizure control but they should by no means be taken to imply a low risk in others. Females with chronic epilepsy are also at risk of sudden death and are equally represented in the studies reported here.

5.5.3 Years of Epilepsy

The literature suggests that patients with recent onset epilepsy are more at risk. This conclusion is mainly based on data from the Cook county series where in 51/51 cases in whom the information was available epilepsy duration was 10 years or less with a mean age at death of 35 years (Leestma et al 1989). Mean duration of epilepsy in the series reported by Earnest et al (1992) which included 39 adults (19-58) was 10 years. Mean duration of epilepsy in the outpatient cohort was 20.8 years with onset in childhood in all cases. Similarly mean duration of epilepsy in the St Elizabeth cohort was 17 years. Among cases in the interview study mean duration of epilepsy was 12 with a wide range (1-29). These findings support the view already stated that in chronic epilepsy, it is age (young

adult) rather than epilepsy duration that defines risk.

5.5.4 Seizure Type

In the vast majority of SUDEP cases reported in the literature a history of TCS is obtained. Exceptions are reported (Dasheiff 1991). Among the cases in the interview study only one did not have a clear history of relatively recent TCS, with the last likely TCS being at least 20 years before death. This case was atypical in that although known to have been well on the day he was later unexpectedly found dead, post-mortem showed evidence of a previous head injury judged to be a little over one week old (see section 5.5.7, page 182). It is likely however that TCS constitute a much greater risk to life than other types of seizures, although complex partial seizures may not be totally without risk. The risk per TCS is unknown.

5.5.5 Seizure Control

As already discussed, and although cases of sudden death in patients with few seizure do occur, the available evidence supports the view that the less well-controlled the epilepsy the higher the risk. Among the patients who were the subjects of the interviews, some of whom had experienced only a small number of total lifetime generalised tonic clonic seizures, only one was in remission and was in the process of withdrawing medication (table 22, page 127). Of 11 sudden death cases among the outpatient cohort, 10 were considered intractable by their

physician. Although the St Elizabeth cohort largely comprised individuals with intractable epilepsy details of control during the period preceding death was largely unavailable.

5.5.6 Syndromic Diagnosis

5.5.6.1 Difficulties with Classification

In the outpatient cohort, the interview study and the study of ictal recordings, patients were classified according to the 1989 ILAE commission 'Proposal for Revised Classification of Epilepsies and Epileptic Syndromes' based on clinical and electrographic criteria (appendix 7.5). Not all cases could be easily categorized.

Two broad areas of difficulty were encountered. The first concerned symptomatic generalised and localisation related syndromes. Where known focal or multifocal pathology was present, often secondary to an insult to the central nervous system in early childhood, but where the clinical seizure type and ictal EEG changes were those of atypical absence (the term is used here in its broad sense), the classification chosen was that of symptomatic generalised.

The other area of difficulty concerned the category of primary generalised epilepsy. This syndrome as defined at present is unlikely to represent a single disease entity and is more likely to represent a heterogenous group of disorders. Seizure

types may include absences, generalised tonic/clonic seizures or myoclonic jerks. EEG findings include spontaneous generalised epileptic discharges which may be provoked by sleep deprivation, hyperventilation or photic stimulation. Positive family history, morning myoclonus, the occurrence of seizures within 1/2-1 hour of awakening and clinical photosensitivity are supportive features. The presence of symptoms or signs indicative of focal pathology (such as a specific aura or abnormal neuroradiological findings) and the presence of progressive neurological disease are reasons for exclusion. Difficulties arise when features are encountered that are not entirely typical but do not by definition indicate exclusion. Examples of such features include apparent poor response to sodium valproate, relative intractability, stable low average or borderline intelligence quotients or (additional) non-specific focal and often variable EEG disturbances. MRI is not routinely performed in cases with primary generalised epilepsy and it may be that some might later be found to have structural abnormalities such as subependymal heterotopia.

In the absence of consensus guidelines, the approach adopted in this study was to exclude cases with any evidence of clinical focal pathology (including specific auras) even if EEG showed generalised epileptic paroxysms. Such cases were classified as undetermined (both focal and generalised features). On the other hand, features listed above did not exclude the patient from the category of idiopathic generalised epilepsy so long as a) seizure-types were

consistent, b) EEG showed generalised epileptic paroxysms with no significant generalised disturbance of background, c) there was no evidence of progressive neurological disease, and d) available neuroradiology, if any, was normal.

5.5.6.2 Syndromic Diagnosis in Outpatient Cohort & Interview Study

Localisation-related cases were the largest group in the outpatient cohort but this reflected the syndromic diagnosis in the cohort in general. Only one case was classified as primary generalised epilepsy, an intractable case and therefore not entirely typical. A syndromic diagnosis was not available in the St Elizabeth cohort. Among those who were the subject of the interview study, 8/20 cases were classified as having primary generalised epilepsy (table 18, page 123). Of those one had a borderline IQ but was otherwise typical and had previously responded to sodium valproate. Of the remaining 7 cases, in addition to EEG reports of generalised spike/wave paroxysmal discharges in all, three were also reported to have focal abnormalities. The clinical presentation however did not include any focal features. It is worth emphasizing that patients with uncontrolled primary generalised epilepsy (unless they have absences only) are also at risk of sudden death. Such cases are all the more regrettable because of the potential for good control. Only 3/8 patients with primary generalised epilepsy in the interview study were on valproate at the time of death for a variety of reasons (see section 4.2.3.2, pages

128 - 129).

5.5.7 Other Factors

A number of other possible risk factors may be relevant in individual cases. Excessive alcohol intake for example has already been referred to. Non-compliance as implied by subtherapeutic or absent post-mortem antiepileptic drug levels have also been reported although interpretation of such findings is very difficult as pointed out earlier (section 1.1.8.1, pages 42 - 43). The importance of these and other factors such as prescribed medication changes, including medication withdrawal and sleep deprivation primarily lies in their potential to precipitate seizures. Whether they also predispose to autonomic instability thus increasing the risk of death from seizures is uncertain. Alcohol for example is known to predispose to cardiac arrhythmias (Schuckit 1987). It is also of interest to note that in the study of heart rate changes reported by Blumhart (1986) accelerations in heart rate were less marked in patients on medication as well as in older patients.

Race is highlighted by studies from the United States as a risk factor with Afro-Americans at relatively increased risk (Hirsch & Martin 1971, Leestma et al 1989). The vast majority of SUDEP cases identified in this work were Caucasian reflecting the population served. Whether the reported racial difference in risk across the Atlantic reflects difference in racial

predisposition or socioeconomic factors remains uncertain. Furthermore, characteristics of SUDEP cases as defined in series where noncompliant Afro-American patients with a history of excess alcohol intake are over-represented may not be applicable in other settings.

SUDEP cases have been observed prior to the era of modern antiepileptic therapy and more recently with a number of different antiepileptic drugs. While acknowledging that specific and probably rare instances occur where a drug may be implicated (for example heart block with carbamazepine), it is unlikely that any particular agent can be blamed for the category as a whole.

Regarding mental handicap, although the St Elizabeth cohort with a relatively high incidence of SUDEP cases included individuals with mental handicap, neither the information available, nor the design of the study allow for any conclusions regarding increased risk over and above that defined by other factors already described.

It is interesting to speculate on the possible relationship between sudden epilepsy deaths and head injuries. Although not considered the direct cause of death in either, there was definite evidence of head injury in two SUDEP cases. Both had been well on the day of death, but at post-mortem had evidence of previous though relatively recent head injury. In neither case was this considered to be the direct cause of death. One

of these cases was included in the interview study (section 4.2.3.2, page 129) and the other in the outpatient cohort (section 4.1.1.4, page 106). Of possible relevance to these observations are the results of a post-head injury study reported by Gastaut & Gastaut in 1957. They observed the occurrence of syncope as a consequence of head injury in 5.6% of cases which was twice as common as epilepsy. Syncope occurred within a few weeks of head injury in three quarters of cases. Vagal hyperreactivity was demonstrated on testing the oculocardiac reflex in 20% of cases with bradycardia/sinus arrest provoked by ocular compression. Positive tests were obtained if testing was performed soon after the injury or around the time when syncope occurred. Although this is a usually a benign and transient phenomenon, it may be that patients with known epilepsy are more at risk of ictal bradycardia/sinus arrest following a head injury particularly during the first few weeks.

5.6 The Unwitnessed Nature of Most SUDEP Cases

As has already been discussed the evidence presented supports the view that the majority of SUDEP cases are seizure-deaths. Yet, of those in the interview study fulfilling the definition of SUDEP, only one of 20 cases was witnessed. It could be argued that this may be due to the selection bias inherent in self-referral. However in both the outpatient cohort and the St Elizabeth cohort such was also the case (sections 4.1.1.4

& 4.1.2.3, pages 108 & 114). In the outpatient cohort, at least 8/11 were unwitnessed. Of the remaining three cases, information was not available or incomplete in two and the onset of the collapse was unwitnessed in the third. In the St Elizabeth cohort, information was not available in 2/14 cases and death was unwitnessed in 10. In one of the remaining two cases, a partner, who had learning difficulty, assumed the person was asleep following a seizure. In another, the onset of collapse was not documented.

The literature is largely in agreement with these observations although the percentage of witnessed deaths varies between studies (3-43%). Schwender & Troncoso (1986) reported only one witnessed death among 29 cases (3.4%). Terrence et al (1975) reported 9 patients dying "*as a result of a single seizure or a few seizures in the presence of witnesses*" among 37 cases (24.3%). Lip & Brodie reported 3/12 (25%) witnessed deaths (only one was seen to have a TCS immediately before death). Leestma et al reported 23/60 (38%) cases where the collapse was witnessed of whom 14 had a witnessed seizure. In a mortality study in children, Harvey et al (1993) observed 59/93 deaths to be unrelated to epilepsy, 14/93 undetermined and 20/93 epilepsy-related. Among these 20 cases there were 11 SUDEP cases who died in bed during sleep and one witnessed seizure (1/12 or 8% at most given 14 undetermined cases), the remainder consisting of cases of drowning (3), acute aspiration (4) and accidental injury (1). Jick et al (1992) reported 11 sudden unexplained deaths (3 in the bathtub), at least 10 of whom were

not witnessed. Hirsch & Martin (1971) reported 8/19 witnessed cases (42%). Dasheiff (1991) reported 3/7 (43%) witnessed cases. Earnest et al (1992) reported on 44 cases of whom only 4 were fully witnessed (9%). Three had generalised convulsions and died. In seven other cases, the onset was not witnessed but the person was found within minutes in apparent cardiac arrest.

The St Elizabeth cohort was of particular interest in this regard. Of note is that no SUDEP cases were observed while the children were under the supervision of the school during the study period. Only one death and one terminal collapse occurred; one child died in a well-documented acute asthmatic attack in the school and another had serial seizures and was transferred to hospital to die some 6 weeks later without regaining consciousness. 14 SUDEP cases occurred after leaving school or on leave at home. Although, taking into account the person years involved, the difference does not reach statistical significance (P = 0.075, section 4.1.2.3, page 117), the trend does raise the possibility that the school with its close supervision and experience in dealing with epilepsy provides some protection despite the fact that most of the children have severe chronic epilepsy. There is an on-call resident staff-nurse for example and 4 other rotating staff present every night looking after the 60 or so pupils at any one time. Regular checks along with a sound monitoring system for each bed help in identifying seizures. If any occur, staff adjust position, ensure adequate respiration, perhaps stimulate

the child, and stay with him/her until judged to be stable. The nurse will also administer medication to end prolonged seizures. Thus, in addition to good compliance with medication, there is an immediate staff response to seizures. Other than the more obvious scope for prevention of seizure-related injury and intervention to avoid prolonged seizures, it may be that timely assistance may restore stable respiratory function. 'Smother proof pillows' are also used at the school. Although suffocation may be a contributory factor in some cases, such pillows, if protective, would only be relevant in the minority found face down.

5.7 Perceived Needs of Bereaved Relatives

The interview study allowed for impressions to be formed regarding the support needed by bereaved relatives in this situation, particularly that these deaths occurred entirely unexpectedly and were apparently unexplained on a background of a chronic condition labelled as 'benign' but requiring much input and support.

Many relatives stated that they had either been categorically told, or led to believe, that epilepsy could not be fatal. Almost all stated in retrospect that they would have preferred to know of the possibility of premature death however remote. Many would have preferred to have been given the opportunity to acknowledge epilepsy as a serious condition rather than have

intuitive fears dismissed, although some relatives and indeed patients still harboured such fears despite reassurances to the contrary. Given this background, bereaved relatives felt very isolated in their apparently unexplained loss and feelings of guilt or blame were frequently expressed. Counselling was not usually offered. Contact with the general practitioner and specialist was helpful when it took place but was insufficient or absent in many cases.

These observations have led to the following minimum recommendations:

* that the general practitioner makes early contact with bereaved relatives while at the same time informing other involved health care workers of the unexpected death

* that the specialist addresses a prompt letter of sympathy to the relatives with an open offer of a meeting

* that information about sudden death in epilepsy, the self-help group 'Epilepsy Bereaved'[5], other supporting agencies and counselling services be given as appropriate.

5.8 Potential for Prevention

Contrary to the experience of early physicians, epilepsy has

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[5]Epilepsy Bereaved? P O Box 1777, Bournemouth BH5 1YR

in recent years been perceived as a benign condition. Yet the available evidence, particularly in chronic cases, argues against this view. Treatment has concentrated on achieving seizure-control and more recently improving quality of life. Better survival in chronic epilepsy should also be one of the goals. The important issue of prevention must therefore underline any study of sudden death in epilepsy. While the following issues have already been addressed in more detail in the appropriate sections, it would be useful at this point to summarize main points.

In current literature the phrase sudden unexpected death in epilepsy (with its various acronyms) denotes a mystery. The lack of a working hypothesis of the nature of these deaths precludes a discussion of prevention. A fundamental premise in this work is that the majority of SUDEP cases are seizure-related. Prevention of SUDEP cases must therefore address a) seizure-prevention, and b) immediate response to seizures.

Seizures, particularly tonic clonic, constitute a risk to the individual by a variety of mechanisms and every effort should be made to control attacks whatever the aetiology. Intractability of the condition, insufficient or no treatment, inappropriate treatment, abrupt medication changes, poor compliance and external influences such as alcohol or sleep-deprivation are all relevant in this context. Informed patient participation may optimize chances of success.

Most of these deaths in this and other studies are unwitnessed. There is clearly more than one possible explanation for this observation. No information is available on the amount of time spent alone as compared to that spent in the company of others in these cases. It may be argued that those who died were more likely to spend time alone during the day and/or at night when many such deaths occur; perhaps they were usually unaccompanied when their habitual seizures occurred. While this explanation cannot be refuted at present, an alternative, by no means proven, explanation is that witnessed seizures are less likely to be fatal.

As previously discussed, in addition to prevention of seizure-related injury and intervention to avoid prolonged seizures, positioning and stimulating the patient and clearing the airway may restore stable respiratory function in some patients. The effect of stimulation on the course of a seizure or the post-ictal phase would be difficult to study, although historically, strong olfactory stimulation (and agents that provoke sneezing) have been recommended for some time for the treatment of epileptic attacks (Avicenna 980-1037); furthermore, it is generally recognised that responsiveness peri-ictally may be impaired to different degrees. Positioning the patient is also important. Among those interviewed at least 6 were found in a position which may impair breathing. While central apnoea was more commonly observed in the seizures recorded, these were mainly complex partial in type. Airflow was reduced however compared to respiratory effort following 2/3 generalised

seizures, and one clear episode of obstructive apnoea followed central apnoea in a complex partial seizure, even with the patient sitting in a chair, when the head slumped onto the chest (figure 6, page 135). That bradycardia occurs within the context of apnoea, emphasizes the close interrelation between heart rhythm and respiration. General advice to relatives of patients with epilepsy regarding cardiopulmonary resuscitation is not currently given and should be addressed, particularly the importance of ensuring adequate respiration during or immediately after a seizure.

If timely assistance were to prevent some of these deaths, a conflict would arise between possible prevention of fatalities where risk is small and independence of people with epilepsy. The need for supervision would depend not only on seizure type, severity and frequency or the presence of other disability but also on patient choice. Rather than simply dismiss risks from seizures, wider recognition both by the medical profession and the public that deaths during seizures may occur albeit relatively rarely is advocated. This knowledge has implications to clinical management.

5.9 Future Research

Epidemiology

In most epidemiological studies, selection bias limits general

applicability of results. Furthermore, it is often the case that information is lacking in a significant subgroup of deaths identified casting doubt on the overall validity of results.

Selection bias would present difficulties in any study based on case notification, for example through the British Neurological Surveillance Unit. Hospital clinic staff are often unaware of the death of patients who no longer attend. Five of 24 deaths from all causes (21%) in the outpatient cohort were unknown to clinic staff despite the study only extending over a three year period.

In England and Wales, the vast majority of SUDEP cases are referred to coroners. In this work, only 2 of a total of 44 cases (4.5%) among the different studies were not thus referred. A coroner-based study is therefore likely to be representative. To identify 50 cases in one year, however, a prospective study would need to involve coroners covering a fifth of the population, a major undertaking (see section 5.3.2, page 161 for a conservative estimate of national incidence).

At another level, longer follow-up of the outpatient cohort, with flagging of individuals via the OPCS, would address the question of SUDEP incidence in relation to age. This will be performed.

One area of uncertainty at present relates to risk per seizure.

Cohorts of patients with different epilepsy syndromes are unlikely to be helpful in this regard, and selecting for study cohorts with specific syndromic diagnosis (for example patients with juvenile myoclonic epilepsy) perhaps as part of a general study of prognosis would help in minimizing the effect of other variables.

Circumstances

Another issue that needs to be explored further is how often the unwitnessed nature of these deaths is incidental, and how often it is due to the lack of timely assistance. Social parameters relating to time spent alone at night or during the day need to be explored. Similarly, near-miss SUDEP events is another potentially informative area of study, although definition is difficult. The literature suggests that such cases are rare, but this is not my own impression. A pilot study could be based on interviews of self-referred witnesses. This approach may throw further light on likely mechanisms.

Ictal recordings

More information can be gained from more extensive ictal recordings. Changes observed in complex partial seizures for example may be related to localisation of seizure discharge. Similarly, further recordings in generalised seizures are of interest particularly during the early post-ictal phase. The latter would be a long-term undertaking in any single telemetry

unit as the aim in such units is usually to record complex partial rather than generalised seizures. It is also worth noting that the presence of attending staff makes the situation no longer analogous to unwitnessed seizures.

Other parameters that would aid interpretation of findings include blood pressure measurement and transcutaneous CO2. Does hypoperfusion contribute to seizure termination? Is normal hypercapnoeic respiratory drive overridden during seizures, or does respiration restart as CO2 rises? An oesophageal probe may also be considered. This should be less susceptible to movement artefact and perhaps allow for uninterrupted recordings of cardiac rhythm as well intrathoracic pressure. Although unlikely to be routinely used, it may facilitate understanding of mechanisms involved in selected cases.

It would also be of interest to consider autonomic testing of patients with pronounced bradycardia during seizures as compared to a matched control group in particular in relation to vagal hyperreactivity. Although there is no evidence at present that such patients are more at risk of sudden death, if this were the case, then protective therapeutic manoeuvres may be considered in selected patients.

As stated above, much remains to be studied in this field. Unfortunately, despite its importance, resources are likely to be limited.

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APPENDIX

7. Appendix

7.1 SUDEP - General Information Leaflet

Sudden Death in Epilepsy

The sense of loss experienced when someone with epilepsy suddenly dies is immense, for in addition to the normal grief felt, the unexpected nature of the loss makes it all that more difficult to accept.

If you are in that situation, you are likely to go over the circumstances again and again. How did it happen? Why did it happen? What could have been done?

It may help you to know that you are not alone. Tragically, sudden death among people with epilepsy is a well-documented occurrence. It may happen to one in every 500-1000 people with epilepsy per year, although this figure is only an estimate and may not be accurate; sometimes but not always, it happens during or after a seizure, one that is apparently no different from the usual seizures experienced so many times before; it often takes place at night in bed during sleep.

Why it happens to a few people, who may be relatively young and otherwise healthy, when the majority thankfully remain well, is still unknown. Given the present state of knowledge, it is not possible to predict this uncommon event nor to give categorical advice about prevention. So try if you can to be kind to yourself and others: do not think "had this or that been done, he or she may still be with us today". We simply do not know.

Not being able to do anything about what has passed, however, is not a reason not to look ahead. There is a need for more studies in this vital area: indeed studies are being planned

and you may wish to take part by sharing your own experience when you have had more time to come to terms with your loss.

Another source of distress you may encounter is that many people even within the medical profession, do not know that sudden death may occur in epilepsy. This general lack of awareness has led to a self-help group being formed by people who have suffered in the same way as you. You may wish to make contact with the group, or alternatively, you may wish to be informed of existing counselling agencies.

For more information contact...

7.2 Ictal Recordings - Patient Information Leaflet

Dear sir/madam,

Thank you for agreeing to take part in this study which aims to record the breathing pattern during attacks in epilepsy.

In addition to the usual brain wave (EEG) recording that you are booked to have, we will also be monitoring your respiration. This will be done using external monitors, and no needles will be involved.

These monitors include:

1. a sensor placed near the mouth and nose to monitor the flow of air

2. two belts around the chest and abdomen to record movement while you breath

3. a sensor that is placed on your finger or toe to measure oxygen level in the blood

There is no danger involved in the additional recordings and you are free to have them removed at any time either temporarily or if you decide to discontinue the study. You will be free to withdraw at any stage without giving any reason and without your medical care being affected in any way.

We will also be showing you how the leads can be temporarily disconnected, as can be done with your routine EEG leads, to allow you to move freely when necessary.

If you have any queries about this study, please contact us via extension 8752.

7.3 Questionnaire - Guide for Interviewers

Questionnaire (to be filled in by interviewer)

Thank you for agreeing to take part in our study.

Let me introduce .....

The PURPOSE of this study is to clarify circumstances relating to the tragic sudden death that sometimes occurs unexpectedly among people who have epilepsy.

We are grateful for your help, and for your patience in yet again going over what must be very distressing details.

You can be sure that the information will be used to form an overall picture of the group of people so tragically affected. Personal identifying details will be left out of any future conclusions.

Even so, you are under no obligation to answer all the questions that we ask.

The interview is fairly long and may take over an hour to perform.

Name of person interviewed: _____

I understand that you have also unexpectedly lost someone dear to you who had epilepsy

Relationship to the above: _____

When: _____

Name of late relative/friend: _____

Would you mind if we referred to him as _____

How close was your contact on a day to day basis?

Please specify: _____

Did you and your late friend/relative?
a) regularly share a bed-room
b) live in the same house, but not share the same bed-room
c) not live in the same house, but saw each other at least once a week
d) not live in the same house, but saw each other at least once a month
e) not live in the same house, but saw each other less than once a month
f) other

if other, please specify _____

_____

Let us start with some general information about your late friend/relative:

Age at death:_____

D.O.B:_____

Sex:_____

Race:_____

Occupation:_____

Employment:_____

Was your friend/relative:
a) employed full-time
b) employed part-time
c) self-employed
d) unemployed
e) student
f) other
g) do not know

Address of friend/relative:
_____

_____

Type of accomodation:_____

What about his/her General Health?

-Apart from the epilepsy, Would you describe his or her health as having been:

a)excellent b)good c)poor d)do not know

-Smoking habits:
a) never smoked regularly
b) stopped smoking _____ before death having smoked for_____
c) regular smoker of _____ cigarettes per day for_____
d) other: specify _____
e) do not know

What about weight? Would you describe him/her as having been:

a)slim b)of average weight c)definitely overweight

-Weight: _____ (specify unit)

-Height: _____ (specify unit)

Exercise: _____

- Details of any other illness not related to epilepsy:

Let me ask you about specific diseases:

- Hypertension: a) Yes b) No c) Do not know
- Diabetes: a) Yes b) No c) Do not know

- Please tick box if appropriate regarding heart disease:

Do not know [ ]

IHD : angina [ ]
myocardial infarction [ ]
Valvular heart disease: [ ]
Arrhythmias: [ ]
Heart failure: [ ]

Other 'heart disease' [ ]
please specify and provide details

- Chest Diseases:

- Asthma: a) Yes b) No c) Do not know
if yes, was the asthma active (symptomatic, or requiring regular or intermittent treatment)?
a) Yes b) No c) Do not know

- Chronic Bronchitis: a) Yes b) No c) Do not know

- Other:

-Snoring:
a)Yes, regularly b)No, or infrequently c)Do not know

Please give details:

- Anything else? (other illness):

_____

_____

-What about alcohol: average per week or day if known:

_____

Which would be the most accurate way to describe him/her:

a) teetotaller
b) occasional drinker (< than 4 days a week)
c) regular drinker in moderation (4 or more days a week)
d) regular drinker with occasional excess
e) regularly drinks in excess
f) alcoholic
g) do no know

If necessary, could we get some more information about his/her general health from his/her GP?

Most recent G.P.: Name:_____

Address:_____

Telephone number:_____

Details of the collapse:

Tell us in your own words what happened:

_____

_____

_____

_____

_____

_____

Let us now go over specific details of the event;

- What time of day did the death occur;

- Where did the death occur;

- Please tick one or more of the boxes below as appropriate;

In own home	[ ]
Indoors	[ ]
Outdoors	[ ]
In bedroom	[ ]
In bed	[ ]
In bathroom	[ ]
In shower	[ ]
In bath	[ ]
Watching screen	[ ] please specify _____
At work	[ ]

- What was your friend/relative doing when this happened?

- Was the death witnessed a) Yes, fully
  b) Not at all
  c) Onset not witnessed, but rest witnessed
  d) Do not know

- Witnessed by _____

- Was there a witnessed seizure at the onset or just before the event?

a)Yes b)No c)Do not know

- Description of suspected seizure;

- duration: _____

- Was it a seizure type that had affected him/her before?

a)Yes b)No c)Do not know

- Timing of seizure in relation to death - please select appropriate answer and fill in approximate time(s):

a) same time - patient died during seizure

b) just preceding - seizure terminated but patient died _____ (time) later having not regained consciousness

c) patient began regaining consciousness/ or regained consciousness but died _____ (state time) after end of seizure.

If he/she had fallen asleep again tick box [ ].

d) last seizure not related to death

- Was there evidence of what may have been an unwitnessed seizure? for example a bitten tongue, secretions on pillow, incontinence, a sudden cry?

a)Yes b)No c)Do not know

If yes, please specify:_____

_____

- Was there any evidence of a head or other injury:

a)Yes b)No c)Do not know

If yes, please specify:_____

_____

- Did the seizure occur during sleep? a) Yes b) No c) Do not know

If no seizure occurred, but the collapse was witnessed, please describe what happened if not already described

_____

_____

_____

- Can you comment in anyway about his/her colour breathing or pulse?

_____

_____

_____

- If the event was not witnessed, in <u>what position and where</u> was he/she found? Can you describe his/her appearance?

_____

_____

_____

_____

a) lying on his back
b) lying on his front with his face down
c) lying on his front with his face down
d) lying on his side
e) sitting up
f) other: please specify _____
g) do not know

- Was there anything near his/her face/mouth that could have affected his/her breathing?

_____

_____

Was he asleep when it happened? Why do you think so?

_____

_____

- Other than any seizure related to the death, please describe the <u>seizure frequency in the week prior to death</u>:

a) none
b) 1-2 during the last week, but not during the last 48 hours
c) 1-2 in the last 48 hours before death
d) series of seizures in the 48 hours before death

- Please describe these seizures:

_____

_____

_____

- What about the period preceding the death?

Usual Medication:

_____

_____

_____

_____

_____

General Compliance:

a) excellent
b) good - rarely or infrequently forgot (with or without help/supervision)
c) poor - often forgot
d) did not take medication

Recent Medication Change:

a) recent (last month) change in anticonvulsants prescribed by physician
b) no prescribed change, but patient stopped or reduced anticonvulsants independently
c) no prescribed change but patient increased anticonvulsants independently
d) no recent change, patient usually compliant
e) no recent change, but patient noncompliant
f) recent addition/withdrawal of other medication
g) no changes to my knowledge
h) not in any position to know

please describe any changes including timing :

_____

_____

_____

_____

Alcohol:

a) recent binge (last 3 days)
b) recent abstention (last week) after heavy intake
c) regular heavy intake continued with no change
d) regular light intake continued with no change
e) teetotaller

Describe:

_____

- Any recent stressful life event such as bereavment, redundancy, divorce..

a)yes b)no c)do not know

please describe:

_____

_____

Was he generally happy and well adjusted? psychiatric history:

a)Yes b)No c)Do not know

Please specify:

_____

_____

- please tick box if appropriate:

Attempted suicide: [ ]
Number:_____
Date of last attempt:_____
Method:_____

Depression requiring medical treatment: [ ].
Dates:_____

- Was there any history of any drug abuse?

a) yes b) no c) do not know

_____

_____

<u>Previous History of Epilepsy:</u>

- Date of onset of seizures (excluding Febrile Convulsions):

_____

a) not previously diagnosed: witnessed seizure at death was the first
b) first seizure during the last three months
c) first seizure during the last year
d) first seizure during the last 5 years
e) first seizure during the last ten years
g) first seizure at least ten years ago
f) seizures on and off since childhood

- Febrile Convulsions: _____

- specialist(s) looking after him?
Name: _____

Address: _____

Telephone number: _____

Hospital number: _____

OTHER: _____

_____

May we contact him for further medical information?

Yes [ ] No [ ]

Was there a cause for the Epilepsy:

_____

Was there any handicap associated with the epilepsy: _____

_____

_____

Seizure Type: a) one type b) more than one type
(please state if daytime or nocturnal)
Describe:
1. _____

_____

_____

2. _____

_____

_____

3. _____

_____

4. _____

_____

Frequency of each type:

a) daily:
b) more or = than once a week (but not a)
c) more or = than once a month (but not b)
d) more or = than once every three months (but not c)
e) more or = than once a year (but not d)
f) more or = than once every two years (but not e)
g) more or = than once every five years (but not f)
h) less than once every five years.
i) do not know

1. a b c d e f g h i

2. a b c d e f g h i

3. a b c d e f g h i

4. a b c d e f g h i

Total n: 1 gM Kleiren
0 = none.
1 = 1 — 10
2 > 10 < 100 .
3 > 100

Previous investigations:

CT: a)Yes b)No c)Do not know

date(s):

Hospital:

---

result

EEG: a)Yes b)No c)Do not know

date(s):

Hospital:

---

result

MRI: a)Yes b)No c)Do not know

date(s):

Hospital:

---

result

- Family History of epilepsy: Yes [ ] No [ ] UK [ ]

specify:_____

_____

- Family History or sudden death: Yes [ ] No [ ] UK [ ]

specify_____

·Was an examination of the body performed? Yes [ ] No [ ] UK [ ]

Where?_____

Do you know the result:_____

_____

Anticonvulsant levels_____

Death Certificate:_____

Coroners Conclusion:_____

Is there anything else you'd like to tell me about, either about the event itself, or how you feel about it, or whether any more could have been done at the time to help you come to terms with what happened?

_____

_____

_____

- You are now aware of the increased risk of SUD that applies to some people with epilepsy,

Would you prefer to have known about it in advance? Yes [ ] No [ ] UK [ ]

What about him/her? Yes [ ] No [ ] UK [ ]

Thank.....Any objection if you were approached again if any details need clarification?

a)Yes b)No

How may you be contacted?

_____

_____

Arrangements for missing details:

_____

Date of interview: _____ Interviewer:_____

7.4 Related Abstracts and Published Work

Nashef L, Sander JWAS, Shorvon SD. Chapter: Mortality in Epilepsy, Pedley & Meldrum, Churchill Livingstone. Recent Advances in Epilepsy 6 (In press)

Nashef L, Sander JWAS, Fish DR, Shorvon SDS. Incidence of Sudden Unexpected Death in an Outpatient Cohort with Epilepsy at a Tertiary Referral Centre. J Neurol Neurosurg Psychiatry (In press)

Abstracts:

Nashef L, Sander JWAS, Shorvon SD, Fish DR. EEG in Sudden Death in Epilepsy; Electroencephal Clin Neurophysiol 1994;91:23P

Nashef L, Sander JWAS, Fish DR, Shorvon SDS. Sudden Unexpected Death in a cohort of young persons with epilepsy and learning difficulties. Epilepsia 1993;34(6):137-138

Nashef L, Sander JWAS, Fish DR, Shorvon SDS. Sudden Unexpected Death Outpatient Cohort with Epilepsy at a Tertiary Referral Centre. Proceedings of NIH Neuroepidemiology meeting May 1994

Nashef L, Sander JWAS, Garner S, Fish DR, Shorvon SD. Circumstances surrounding sudden death in epilepsy: Interviews with Relatives. Abstracts from the European Congress of Epileptology (1994). Epilepsia 1994;35(7):18

Nashef L, Allen P, Walker F, Sander JWAS, Garner S, Fish DR, Shorvon SD. Ictal and Postictal Respiratory Parameters: Methodology and relation to sudden death in epilepsy American Epilepsy Society December 1994

Nashef L, F Walker, JWAS Sander, DR Fish, SD Shorvon. Apnoea & Bradycardia during Epileptic Seizures: Relation to Sudden Death in Epilepsy. American Academy of Neurology May 1995

7.5 International Classification of Epilepsies & Epileptic Syndromes

The following table is derived from the Proposal for Revised Classification of Epilepsies and Epileptic Syndromes: Commission on Classification and Terminology of the International League Against Epilepsy (Epilepsia 1989;30(4):389-399)

1. Localisation-related
    - 1.1 Idiopathic (with age-related onset)
        - * Benign childhood epilepsy with centrotemporal spikes
        - * Childhood epilepsy with occipital paroxysms
        - * Primary reading epilepsy
    - 1.2 Symptomatic
        - * Chronic progressive epilepsia partialis continua of childhood (Kojewnikow's syndrome)
        - * Syndromes characterized by seizures with specific modes of precipitation
        - * Temporal lobe epilepsies
        - * Frontal lobe epilepsies
        - * Parietal lobe epilepsies
        - * Occipital lobe epilepsies
    - 1.3 Cryptogenic

2. Generalized epilepsies and syndromes
    - 2.1 Idiopathic (with age-related onset)
        - * Benign neonatal familial convulsions
        - * Benign neonatal convulsions
        - * Benign myoclonic epilepsy in infancy
        - * Childhood absence epilepsy (pyknolepsy)
        - * Juvenile absence epilepsy
        - * Juvenile myoclonic epilepsy
        - * Epilepsy with grand mal seizures on awakening
        - * Other generalized idiopathic epilepsies not defined above

* Epilepsies with seizures precipitated by specific modes of activation

2.2 Cryptogenic or symptomatic (in order of age)

* West syndrome
* Lennox-Gastaut
* Epilepsy with myoclonic astatic seizures
* Epilepsy with myoclonic absences

2.3 Symptomatic

2.3.1 Non-specific etiology

* Early myoclonic encephalopathy
* Early infantile epileptic encephalopathy with suppression burst
* Other symptomatic generalized epilepsies not defined above

2.3.2 Specific syndromes

3. Epilepsies and syndromes undetermined whether focal or generalized

3.1 With both foal and generalized features

* Neonatal seizures
* Severe myoclonic epilepsy in infancy
* Epilepsy with continuing spike-waves during slow-wave sleep
* Acquired epileptic aphasia (Landau-Kleffner-syndrome)
* Other undetermined epilepsies not defined above

3.2 Without unequivocal generalized or focal features

4. Special syndromes

4.1 Situation-related seizures

* Febrile convulsions
* Isolated seizures or isolated status epilepticus
* Seizures occurring only when there is an acute metabolic or toxic event due to factors such as alcohol, drugs, eclampsia, nonketotic hyperglycaemia